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(54) **METHODS AND SYSTEMS FOR ASSESSING MUSCLE ELECTRICAL ACTIVITY IN RESPONSE TO STIMULATION OF A MOTOR NERVE**

(71) Applicant: **T4 Analytics LLC**, Dover, DE (US)

(72) Inventors: **David Robert Hampton**, Woodinville, WA (US); **Vincent C.M.H. Larik**, Kerkrade (NL)

(73) Assignee: **T4 ANALYTICS LLC**, Dover, DE (US)

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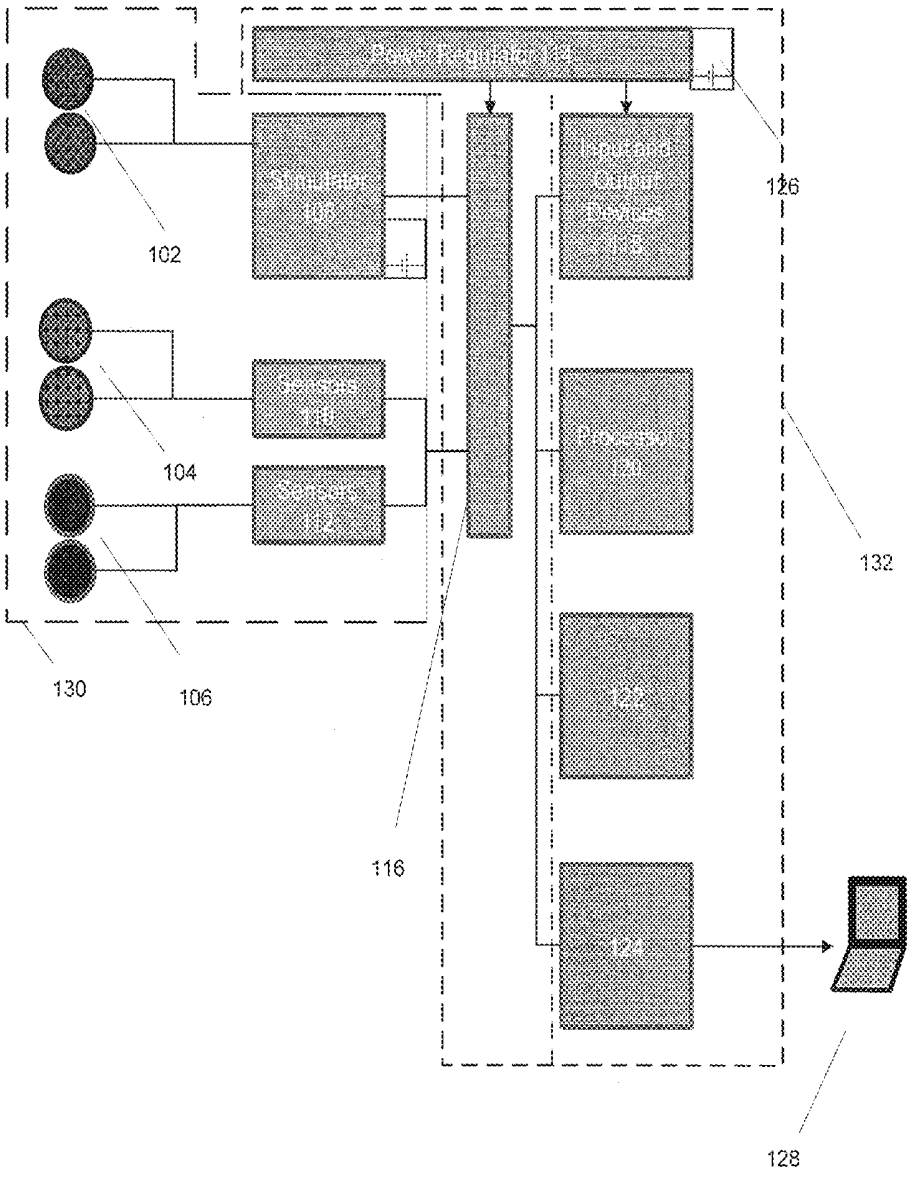
USPC **600/546**

(57) **ABSTRACT**

Provided are systems, devices and methods for monitoring anesthesia. For example, the methods, devices and systems are optionally used to assess muscle electrical activity in response to stimulation of a motor nerve.



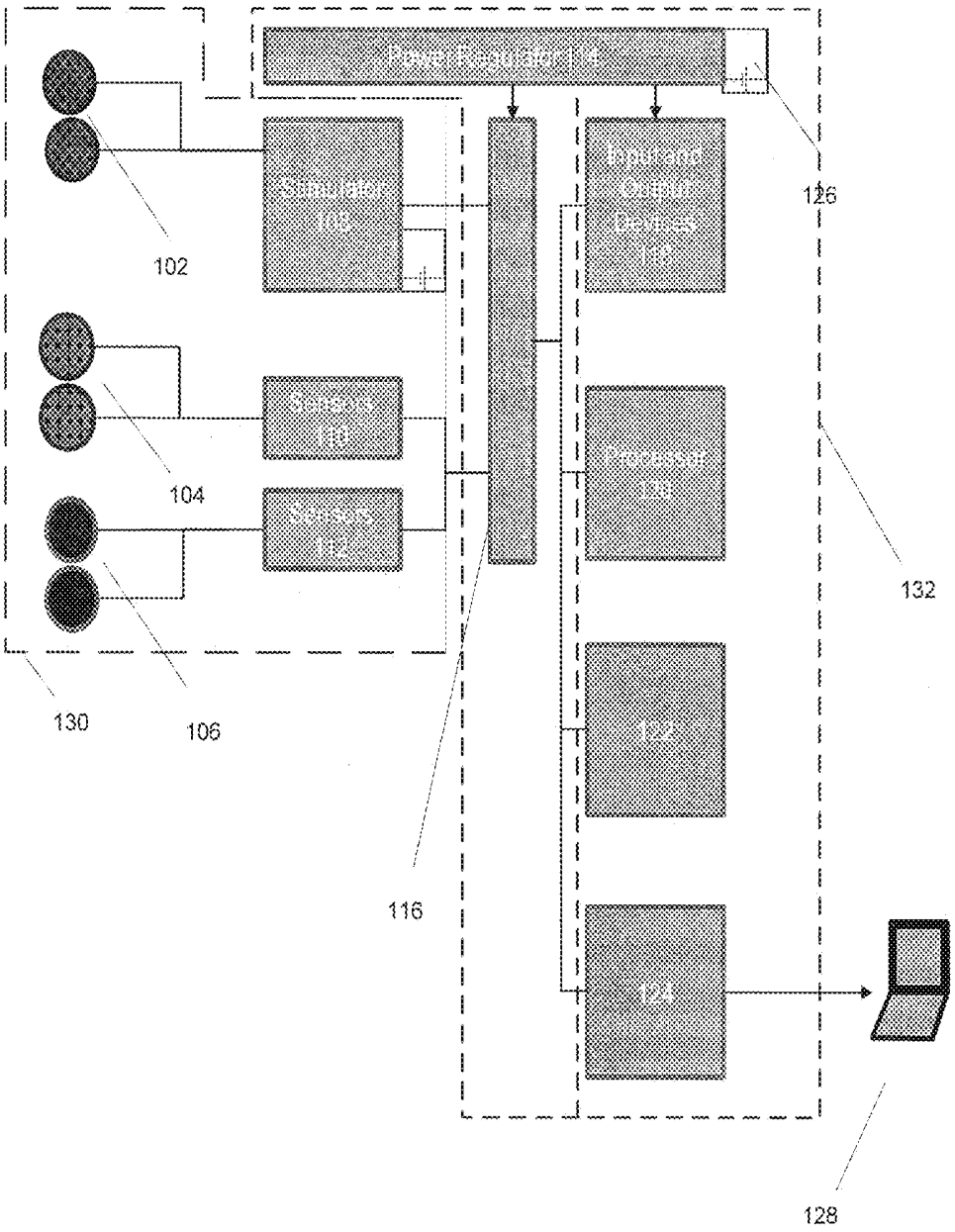

Power Regulator 114
Simulator 108
Inputand Safety Devices 112
Sensors 110
Sensors 110
Processor 120
122
124
102
104
106
116
126
128
130
132

FIG. 1

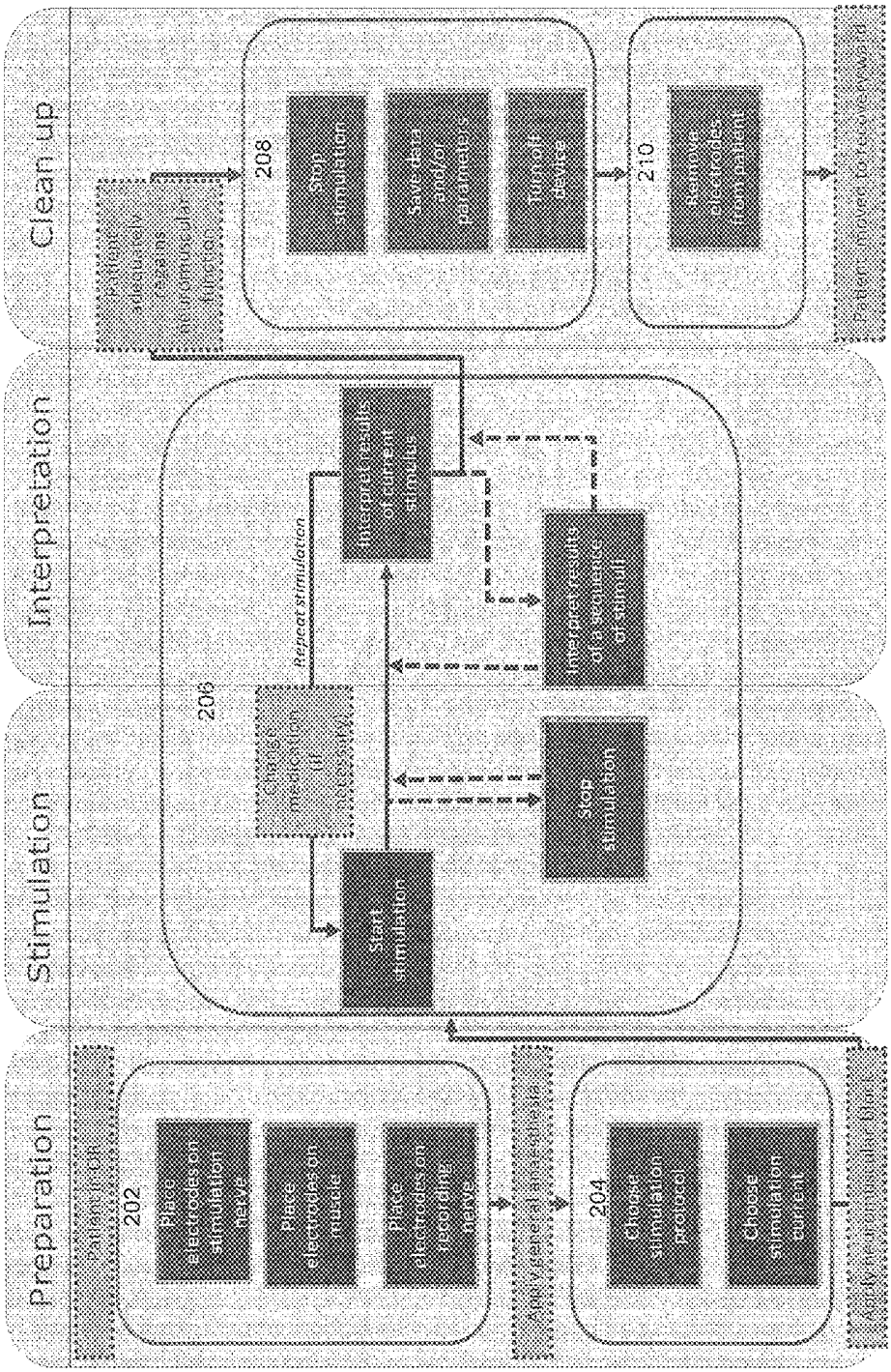

Preparation
Stimulation
Interpretation
Clean-up
202
Place electrodes on stimulation leads
Place electrodes on nerve
Place electrodes on recording leads
204
Choose stimulation protocol
Choose stimulation current
206
Start stimulation
Stop stimulation
Interpret results of current stimulus
Interpret results of sequence of stimuli
208
Stop stimulation
Save data and/or parameters
Turn off device
210
Remove electrodes from patient

FIG. 2

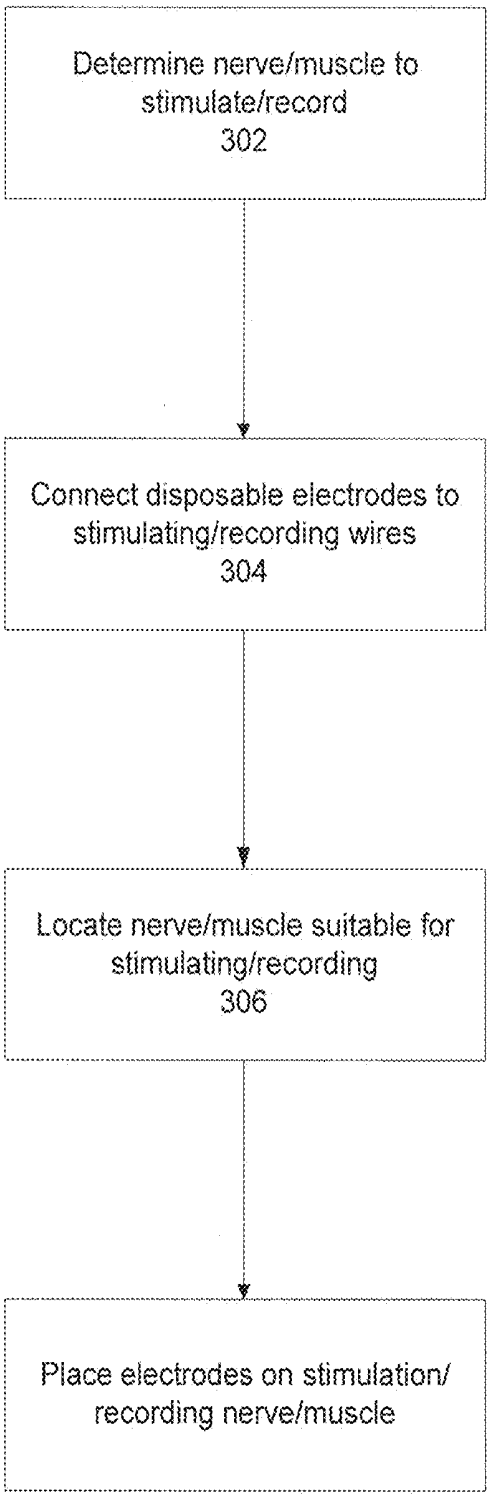

Determine nerve/muscle to stimulate/record
302
Connect disposable electrodes to stimulating/recording wires
304
Locate nerve/muscle suitable for stimulating/recording
306
Place electrodes on stimulation/ recording nerve/muscle

FIG. 3

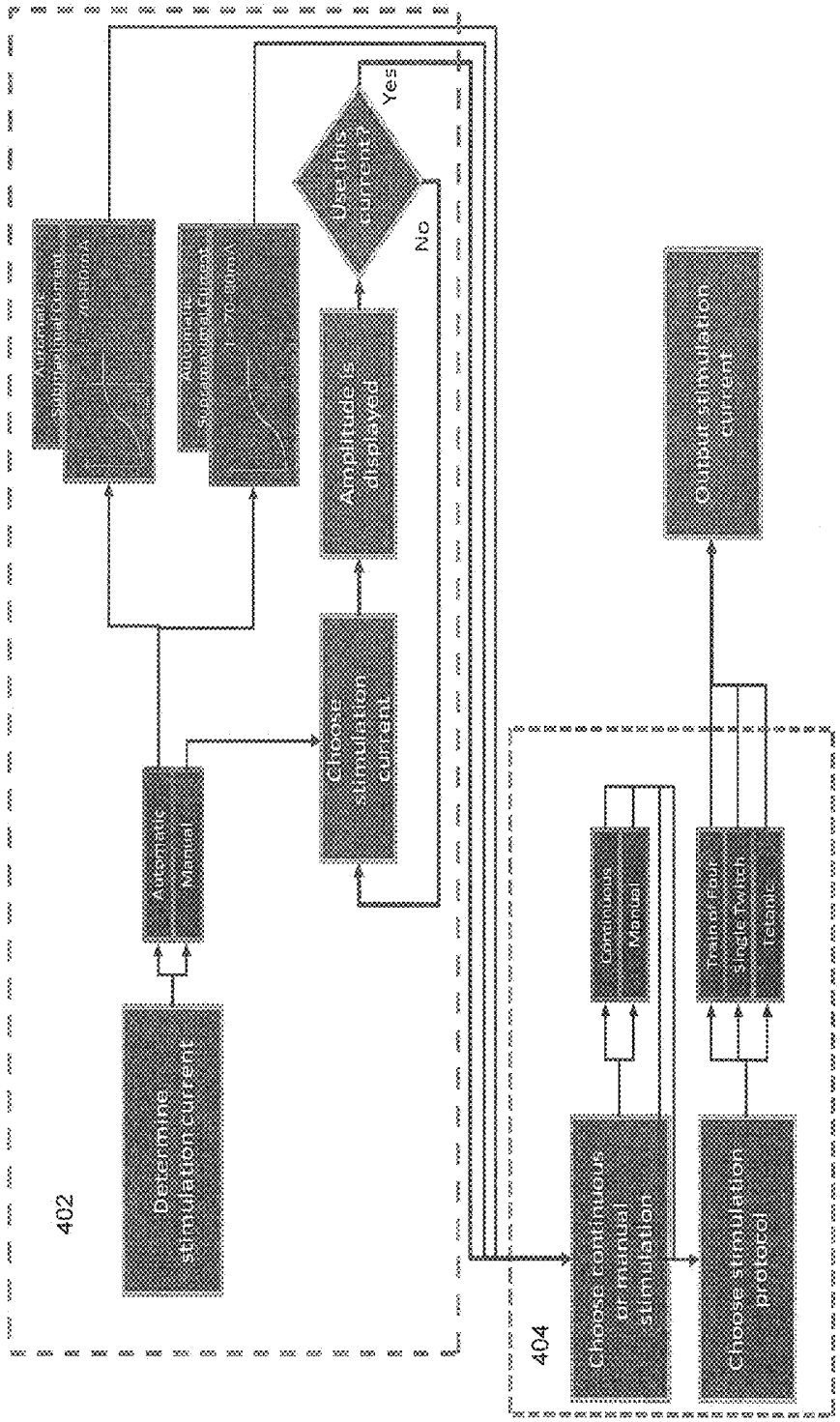

402
Determine stimulation current
Automatic
Manual
Choose stimulation current
Amplitude is displayed
Yes
No
404
Choose continuous or manual stimulation
Choose stimulation protocol
Continuous
Manual
Train of Four
Single Twitch
Tetanic
Output stimulation current

FIG. 4

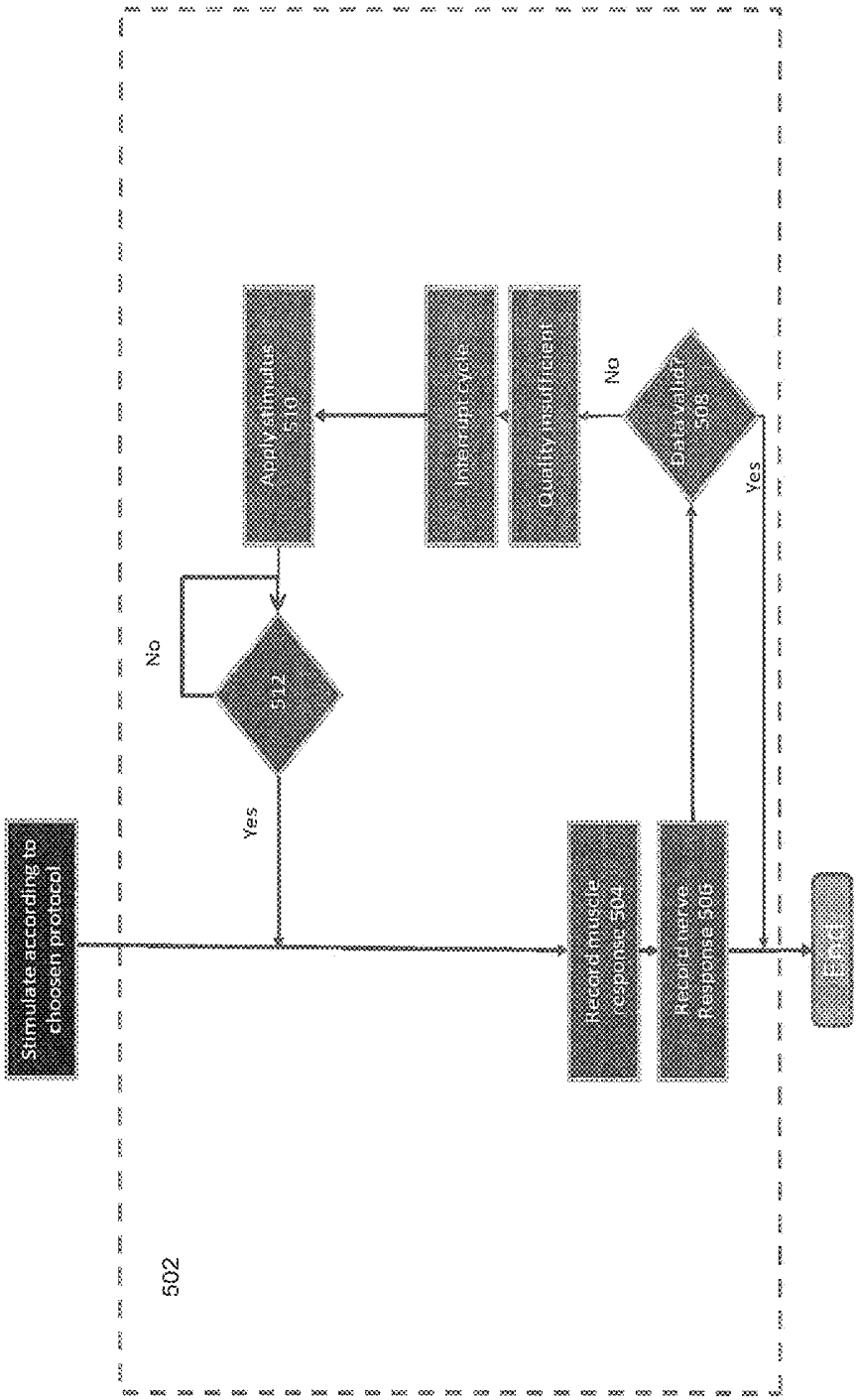

Stimulate according to chosen protocol
512
No
Yes
Apply stimulus 510
Increase cycle
Quality insufficient
Data valid? 506
No
Yes
Record muscle response 504
Record next response 508
End
502

FIG. 5

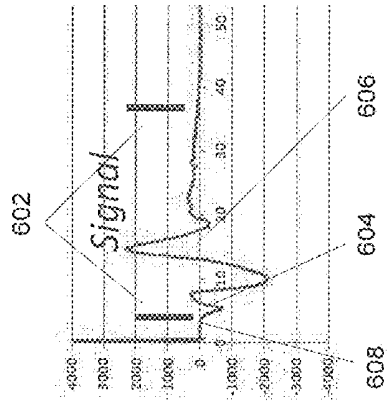


FIG. 6C

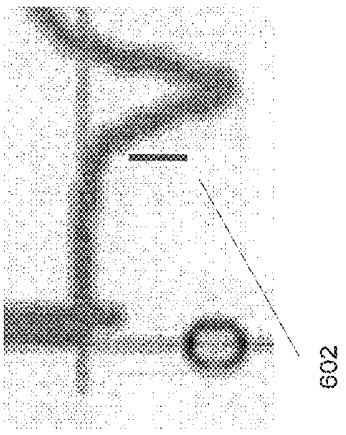


FIG. 6B

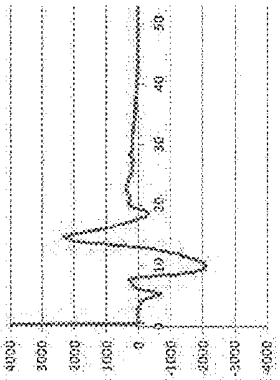


FIG. 6A

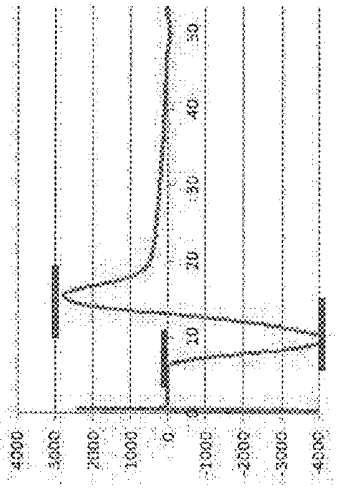


FIG. 6F

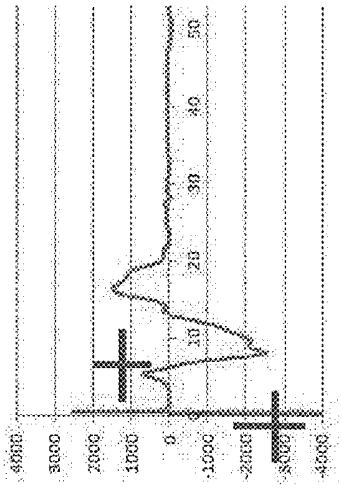


FIG. 6E

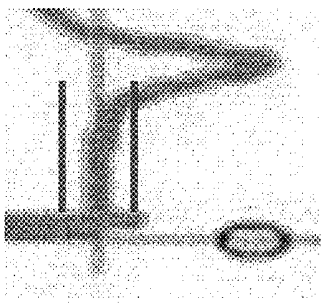


FIG. 6D

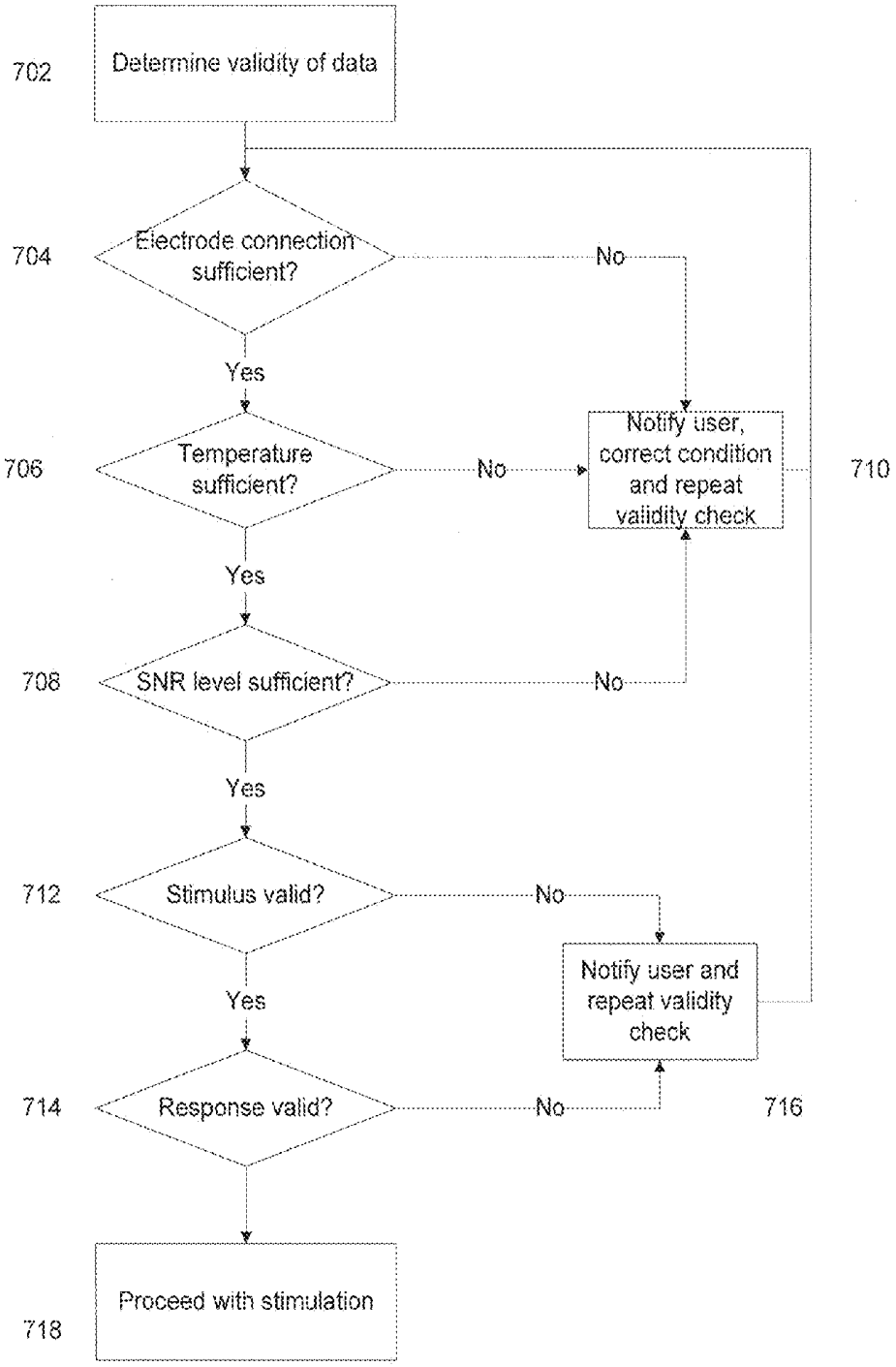

702
Determine validity of data
704
Electrode connection sufficient?
No
Yes
706
Temperature sufficient?
No
Notify user, correct condition and repeat validity check
710
Yes
708
SNR level sufficient?
No
Yes
712
Stimulus valid?
No
Notify user and repeat validity check
Yes
714
Response valid?
No
716
Proceed with stimulation
718

FIG. 7

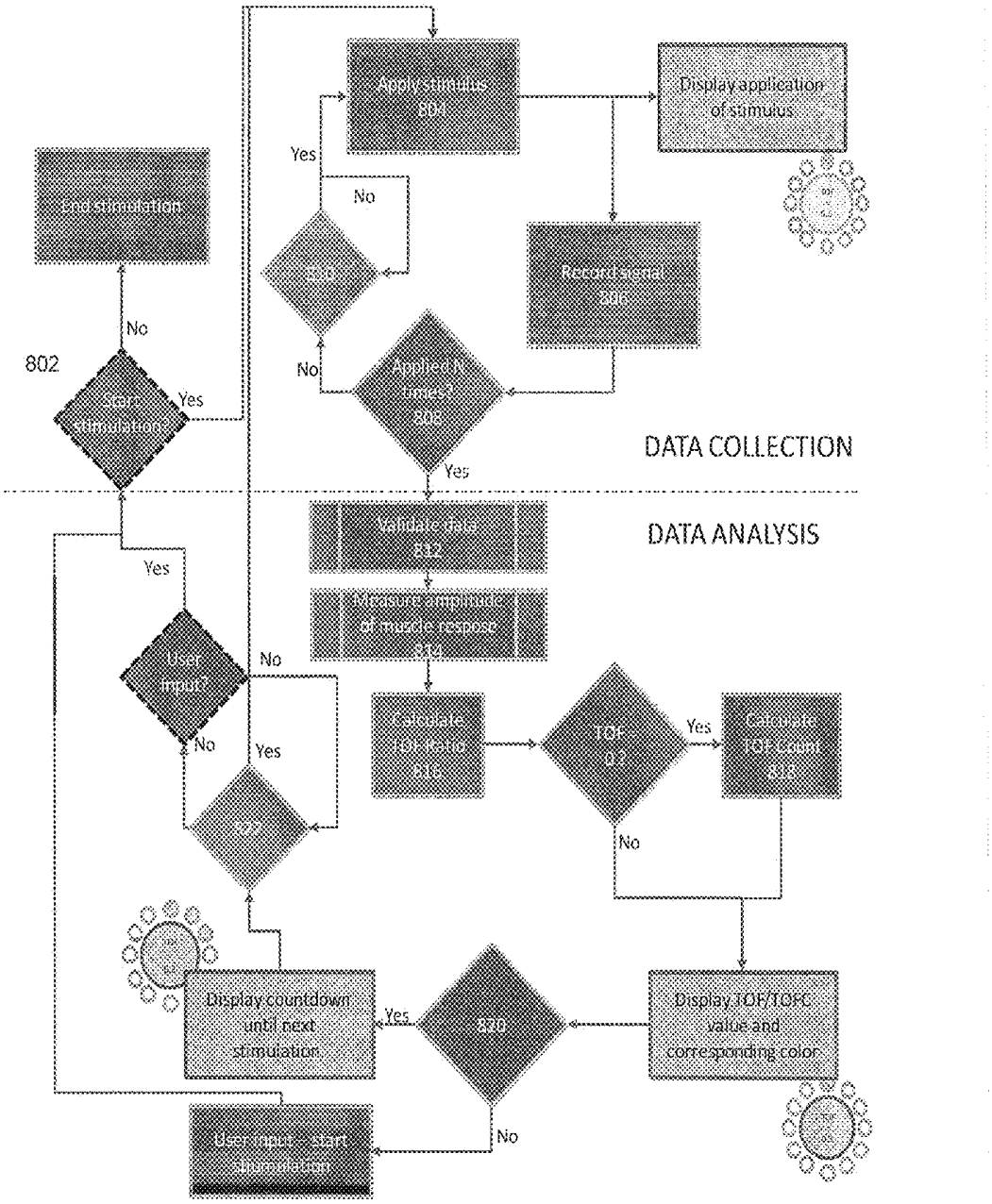

Apply stimulus 804
Display application of stimulus
Yes
No
End stimulation
No
802
Start stimulation?
Yes
Record signal 808
No
Applied N times? 806
Yes
DATA COLLECTION
DATA ANALYSIS
Validate data 812
Measure amplitude of muscle response 814
Yes
User input?
No
No
Yes
Calculate TOF ratio 816
TOF 0.7
Yes
Calculate TOF count 818
No
Display countdown until next stimulation
Yes
820
Display TOF/TOFC value and corresponding color
No
User input - start stimulation

FIG. 8

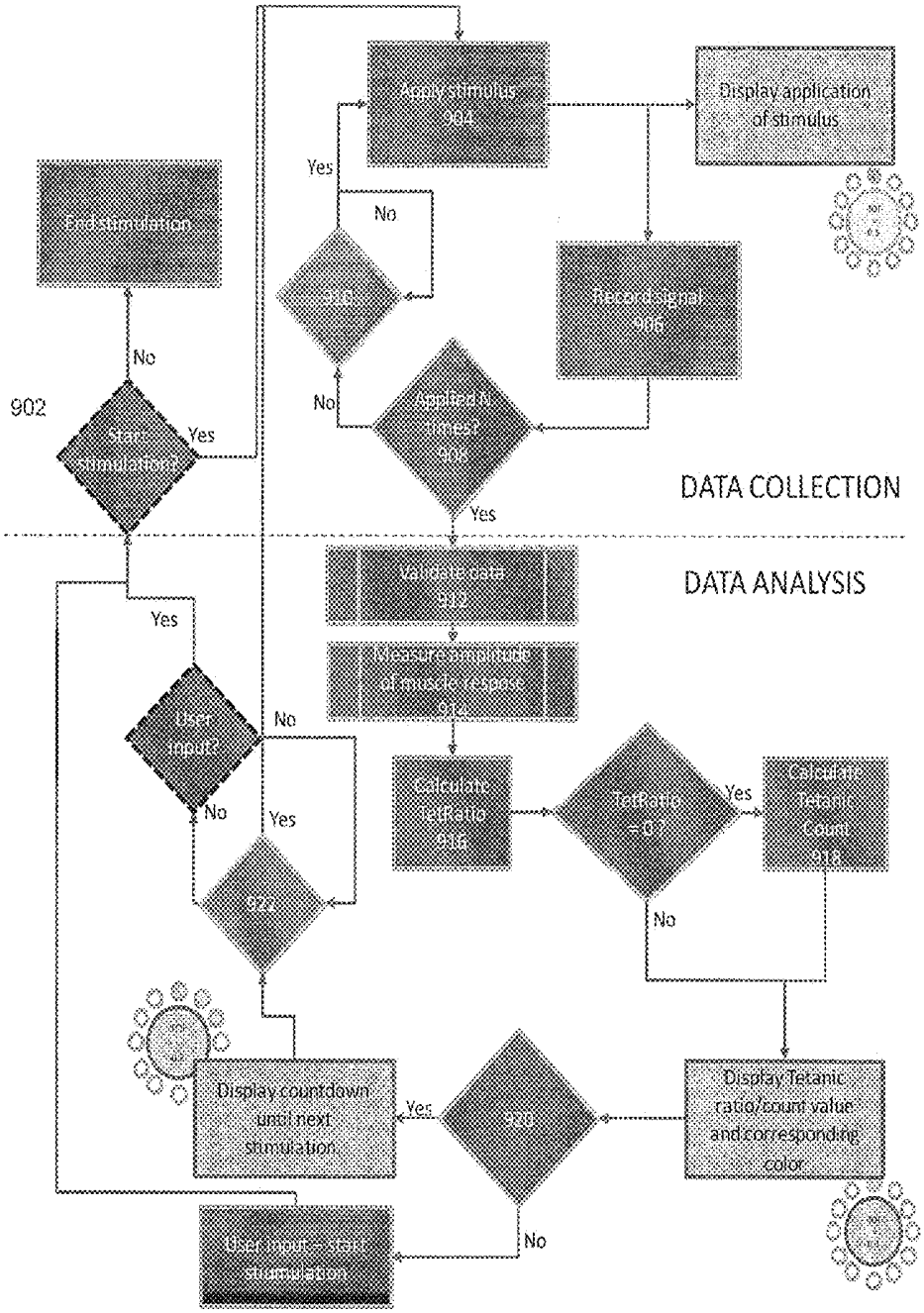

Apply stimulus 904
Display application of stimulus
Yes
No
End stimulation
Record signal 906
No
902
Start stimulation
Yes
No
Applied N times? 908
DATA COLLECTION
Yes
Validate data 910
DATA ANALYSIS
Measure amplitude of muscle response 912
Yes
User input?
No
No
Yes
Calculate tetanic ratio 916
Tetanic ratio = 0?
Yes
Calculate tetanic count 918
922
No
Display countdown until next stimulation
Yes
924
Display Tetanic ratio/count value and corresponding color
User input = Next stimulation
No

FIG. 9

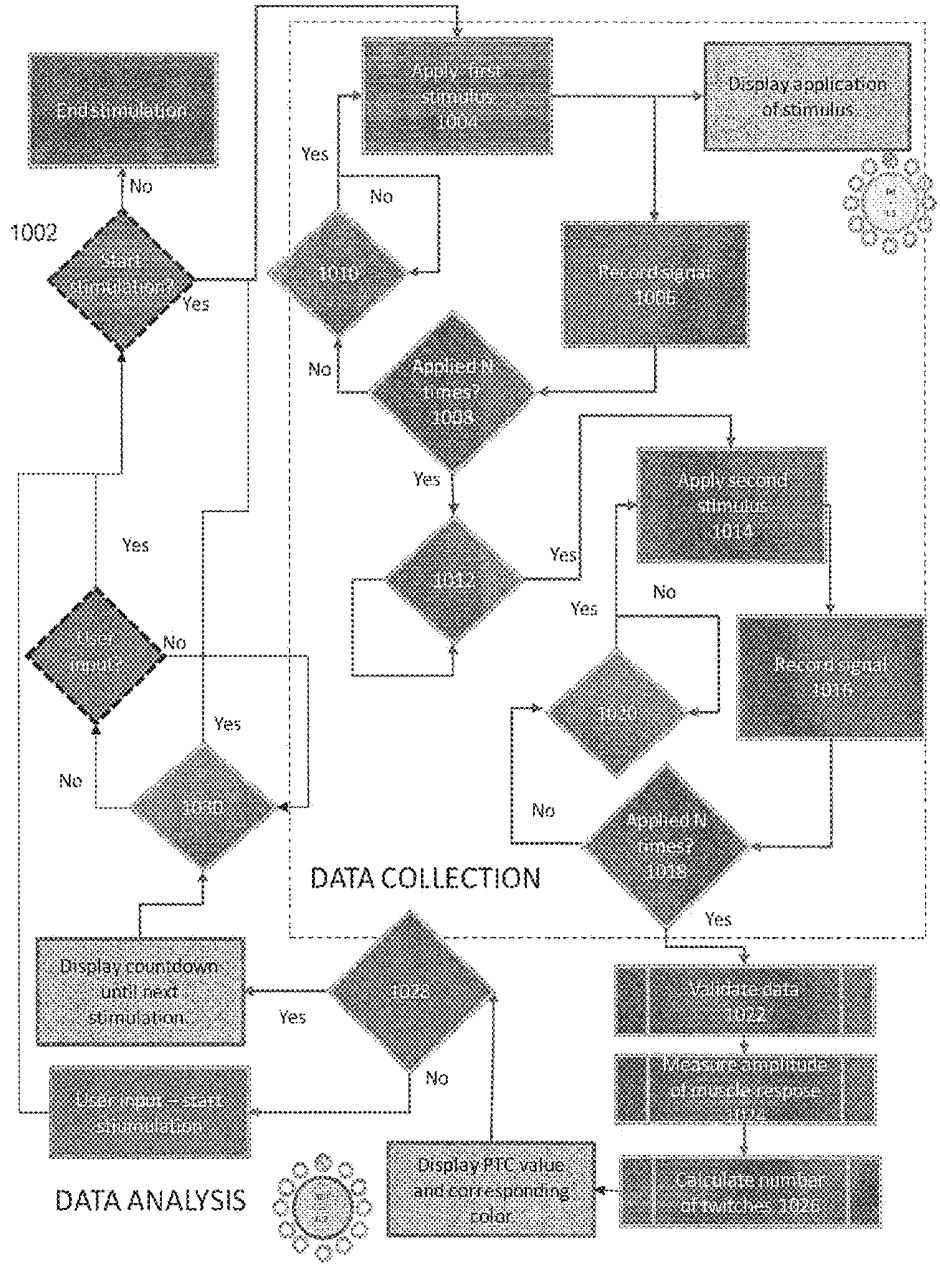

End stimulation
No
1002
Start stimulation?
Yes
Apply next stimulus 1004
Display application of stimulus
Yes
No
1010
Record signal 100F
No
Applied N times? 1008
Yes
Yes
1012
Yes
Apply second stimulus 1014
No
Yes
1020
No
Record signal 100F
Yes
1018
No
Applied N times? 1016
DATA COLLECTION
Yes
Display countdown until next stimulation
1022
Yes
No
Validate data 1024
Measure amplitude of muscle response 1025
Calculate number of twitches 1026
Display PTC value and corresponding color
DATA ANALYSIS

FIG. 10

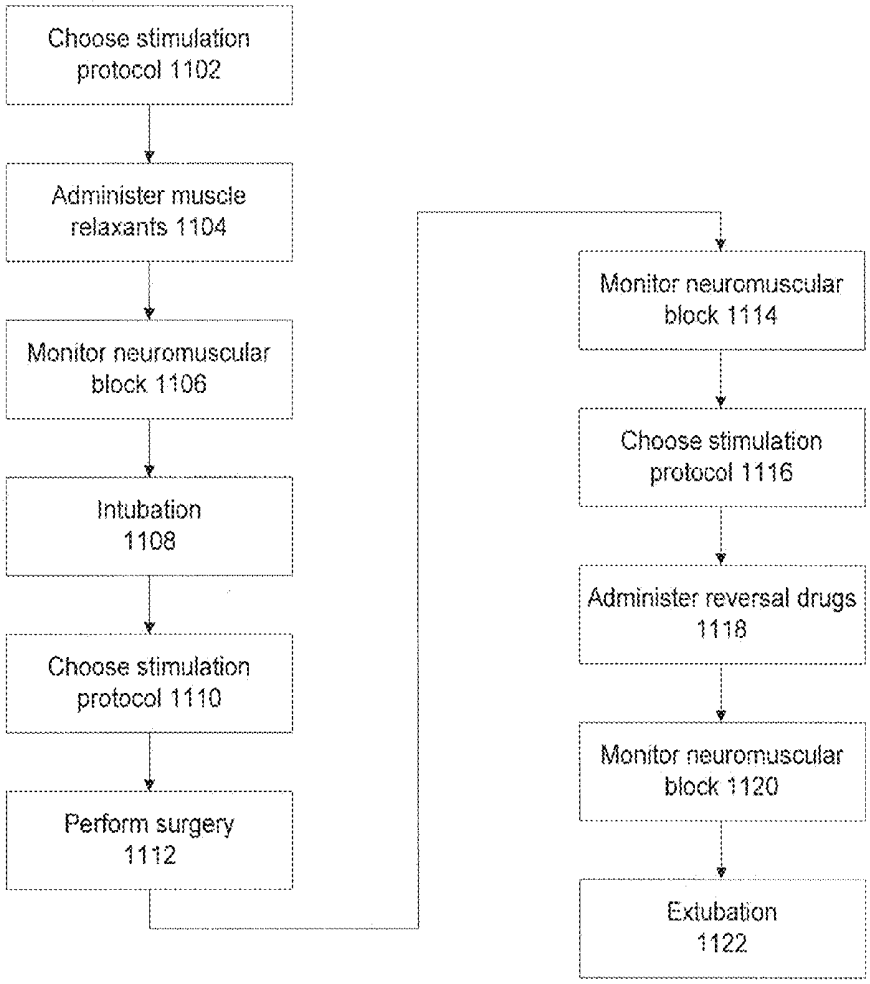

Choose stimulation protocol 1102
Administer muscle relaxants 1104
Monitor neuromuscular block 1106
Intubation 1108
Choose stimulation protocol 1110
Perform surgery 1112
Monitor neuromuscular block 1114
Choose stimulation protocol 1116
Administer reversal drugs 1118
Monitor neuromuscular block 1120
Extubation 1122

FIG. 11

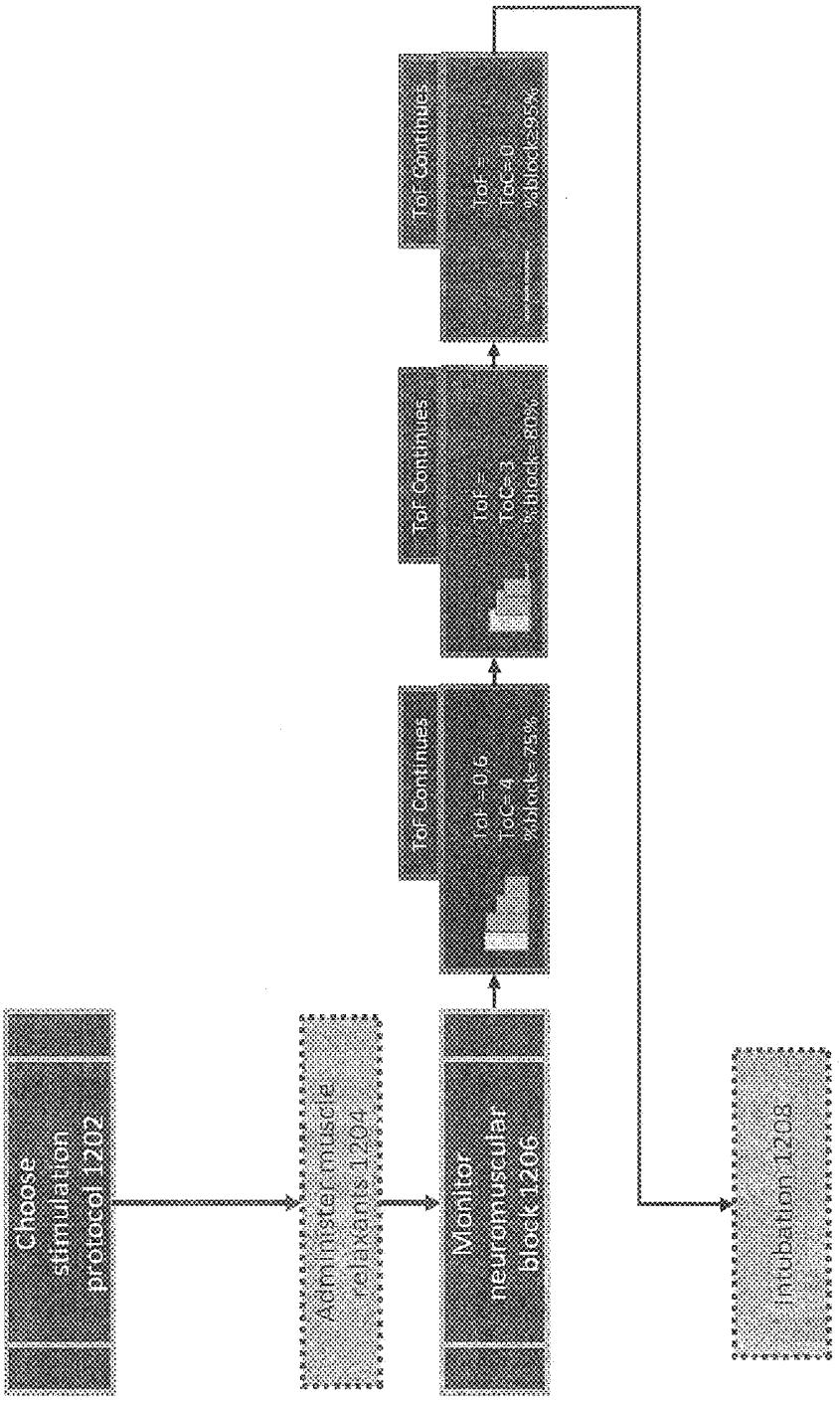

Choose stimulation protocol 1202
Administer muscle relaxants 1204
Monitor neuromuscular block 1206
ToF Continues
ToF = ToC=4 %Block=75%
ToF Continues
ToF = ToC=3 %Block=80%
ToF Continues
ToF = ToC=0 %Block=95%
Intubation 1208

FIG. 12

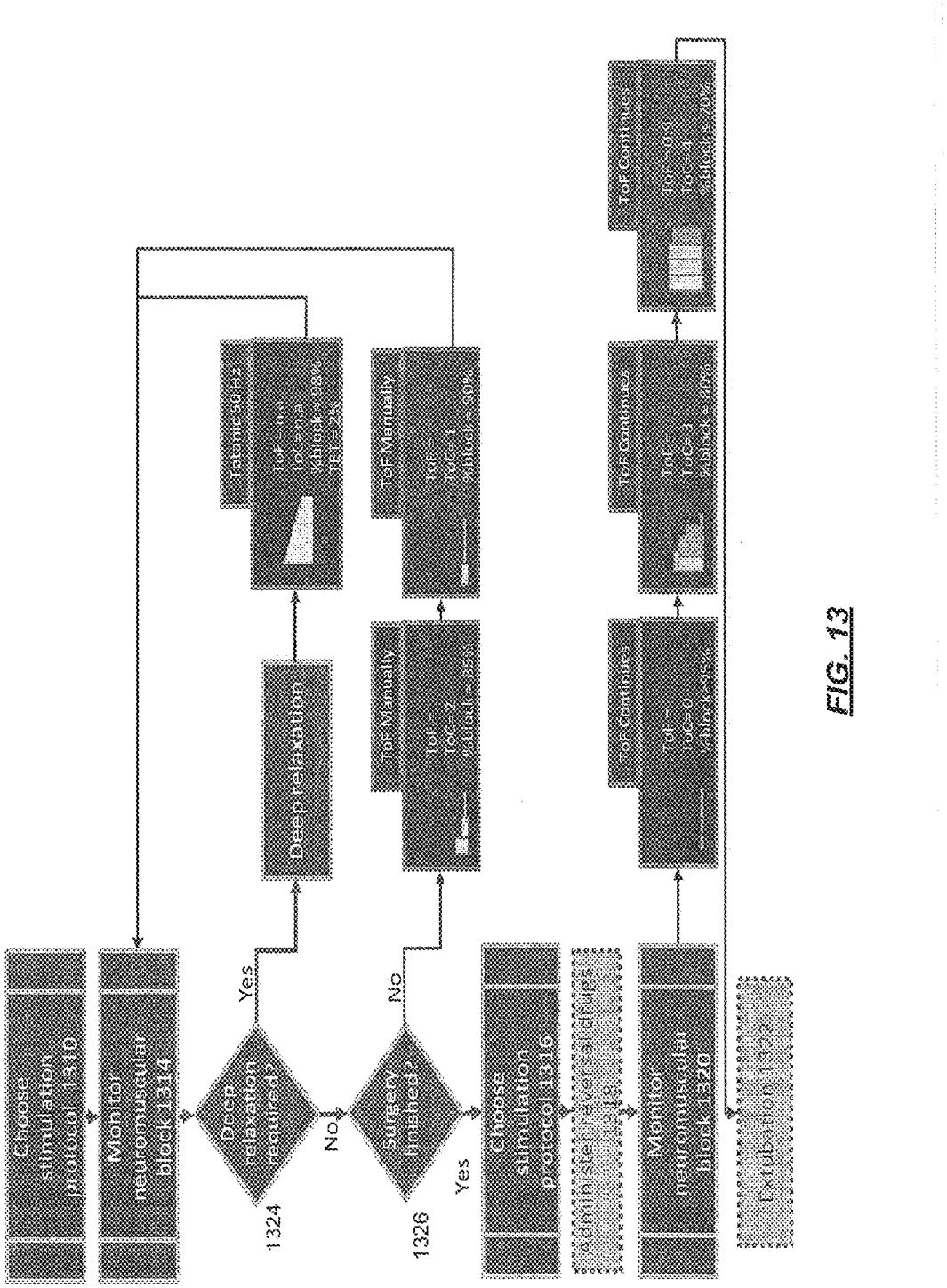

Choose simulation protocol 1310
Monitor neuromuscular block 1314
Deep relaxation required? 1324
Yes
No
Deep relaxation
ToF Manually
ToF Manually
Surgery finished? 1326
No
Yes
Choose simulation protocol 1316
Administer reversal drug 1318
ToF continues
ToF continues
ToF continues
Monitor neuromuscular block 1320
Extubation 1322

FIG. 13

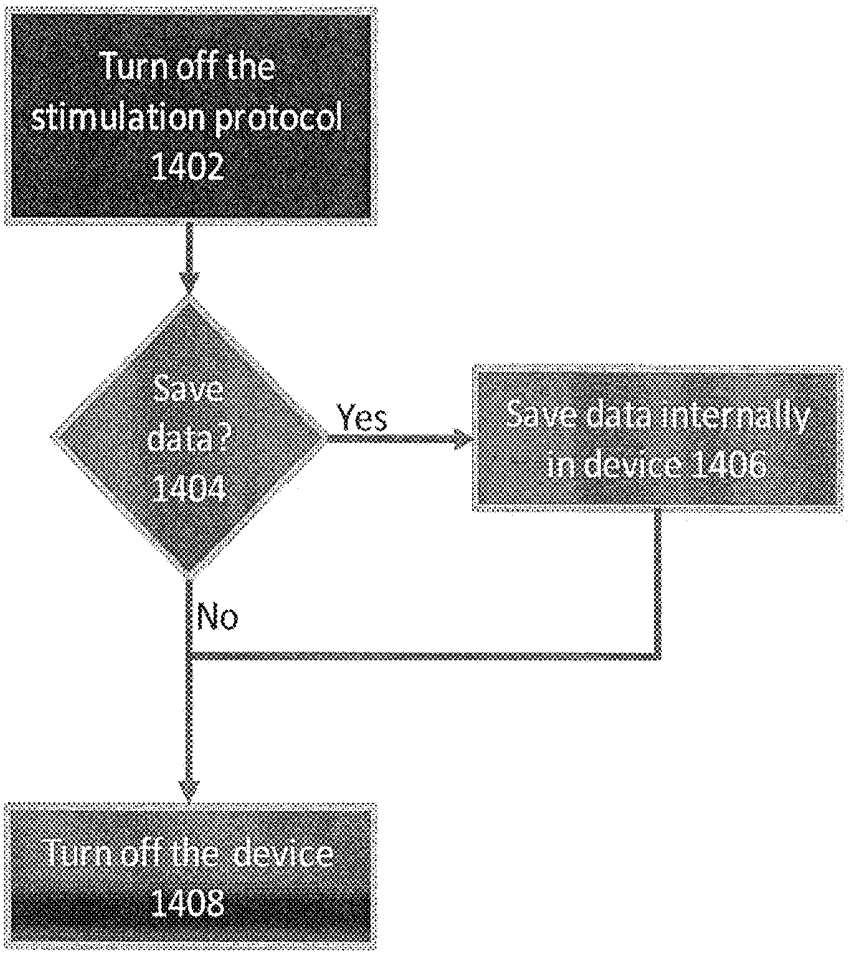

Turn off the stimulation protocol 1402
Save data? 1404
Yes
Save data internally in device 1406
No
Turn off the device 1408

FIG. 14

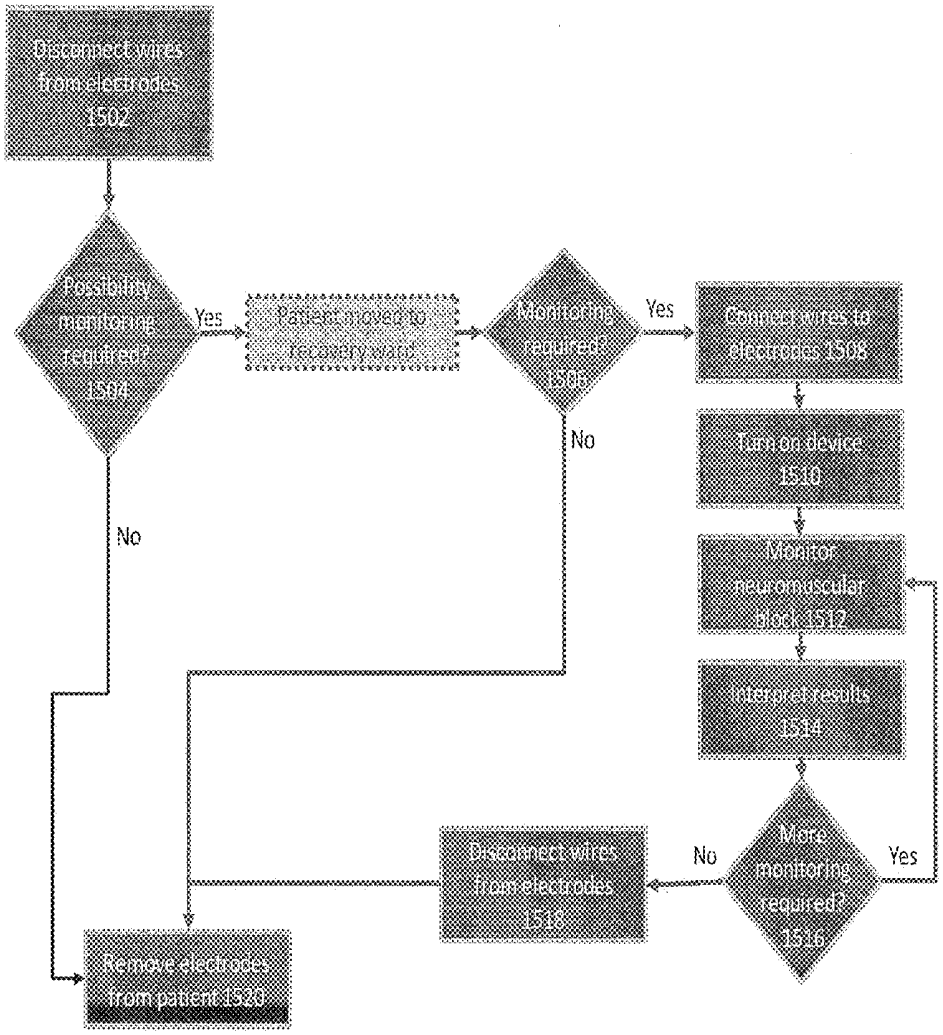

Disconnect wires from electrodes 1502
Possibility monitoring required? 1504
Yes
Patient moved to recovery area
Monitoring required? 1506
Yes
Connect wires to electrodes 1508
Turn on device 1510
Monitor neuromuscular block 1512
Interpret results 1514
More monitoring required? 1516
Yes
No
Disconnect wires from electrodes 1518
No
Remove electrodes from patient 1520

FIG. 15

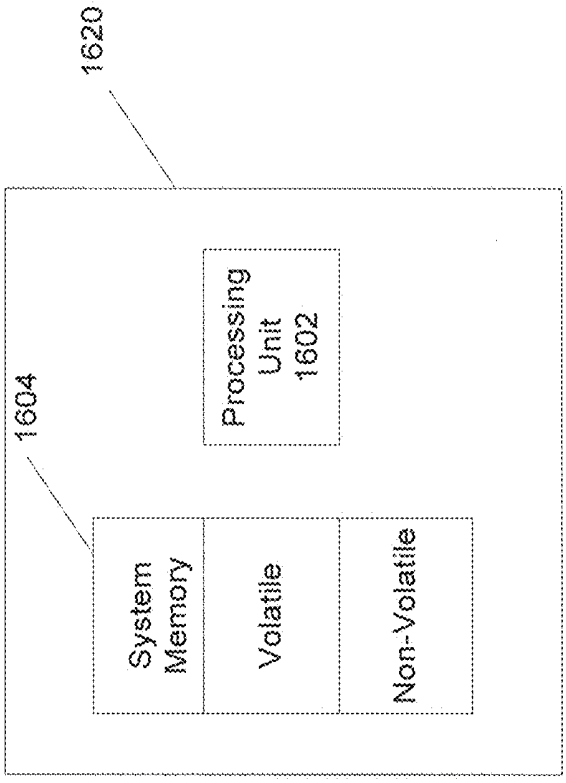

1620
Processing Unit 1602
1604
System Memory
Volatile
Non-Volatile

FIG. 16

METHODS AND SYSTEMS FOR ASSESSING MUSCLE ELECTRICAL ACTIVITY IN RESPONSE TO STIMULATION OF A MOTOR NERVE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 61/591,549, filed on Jan. 27, 2012, entitled "Methods and Systems For Assessing Muscle Electrical Activity in Response to Stimulation of a Motor Nerve," the disclosure of which is expressly incorporated herein by reference in its entirety.

TECHNICAL FIELD

[0002] This document relates to monitoring and assessment of anesthesia levels in subjects.

BACKGROUND

[0003] About 230 million surgeries take place annually world-wide; 40 million US patients undergo in-hospital general anesthesia, which induces loss of consciousness, each year, and 25 million of those also receive muscle relaxants (also called neuromuscular blocking agents, NMBAs), which inhibit neuromuscular transmission. These relaxant agents decrease muscle tension and suppress reflex contractions, and may be administered for several reasons including the following.

[0004] General anesthesia requires that patients' lungs be mechanically (artificially) ventilated via an endotracheal tube (breathing tube, or ETT) that is placed into the trachea (windpipe). This tube must pass down the throat and between the vocal cords, and muscle relaxants make this procedure possible and safer for patients.

[0005] Surgeries involving the abdomen, the lungs and the brain require muscle relaxants (neuromuscular blocking drugs, NMBAs) to allow the surgeon to work and to minimize injury to the patient and to the organs.

[0006] Secondary applications include gynecologic, orthopedic, plastic surgery and laparoscopic procedures, and various procedures performed in intensive care unit (ICU), emergency department (ED) and Ambulatory Care Center (ACC); these procedures require neuromuscular blockade and mechanical ventilation.

[0007] Muscle relaxants (NMBAs) have two forms: depolarizing agents, which are short-acting (5-10 min duration) and are sometimes used at the start of anesthesia to facilitate tracheal intubation, and non-depolarizing agents that have a longer duration of action (20-60 min), and that are used to maintain muscle relaxation during surgery. The effects of non-depolarizing agents start within minutes and continue for up to 20-60 minutes after withdrawal (depending on the type of relaxant used), so they must be administered repeatedly throughout the surgical procedure.

[0008] Drug effects must completely dissipate once the surgical procedure is complete, however, so that patients can start breathing on their own (spontaneously). Reversal drugs (anticholinesterases) can be administered to shorten recovery from muscle relaxants, but reversal drugs can slow the heart to dangerous levels (bradycardia), and can have a host of other unpleasant side effects, such that atropine (or glycopyrrolate) is commonly administered as an adjunct to reversal agents. Unfortunately, atropine and atropine-like agents also have their own additional side-effects, such as nausea, vomiting and tachycardia.

[0009] Overdosing of relaxants to assure complete muscle paralysis during surgery can lead to delayed recovery of muscle function, prolonging recovery room stays, hospital stays and increasing healthcare costs. 30-60% of patients admitted to the postoperative care unit (Recovery Room, or PACU) have significant residual muscle weakness (i.e., incomplete reversal of paralysis). In extreme cases, patients can experience a Critical Respiratory Event (CRE) in which they are unable to breathe independently. CRE affects 0.8% of patients who have residual weakness, and may require emergency placement of another breathing tube; approximately 10,000 patients are estimated to require emergent re-insertion of the breathing tube each year from complications of post-surgical CRE. The need for emergent reintubation leads to morbidity and mortality, and markedly increases the cost of healthcare.

[0010] An optimal dose of paralytic (muscle relaxant) medications should be based on the effect that they have on muscles, rather than dosing based on physical characteristics of the patient (age, sex, weight) or drug concentration (blood or tissue). Unfortunately, simple subjective assessment of muscle tone, spontaneous breathing, and reflex responses are not accurate or consistent indicators of relaxant effect.

[0011] Neuromuscular Monitors have been proposed to give more precise indication of degree of neuromuscular block, but these are hard to use and expensive—in fact, less than 25% of American anesthesiologists use nerve stimulators to test muscle function, and no more than 5% of American anesthesiologists objectively measure the state of muscle reversal.

[0012] Accelerographs and mechanomyographs are neuromuscular monitors that are sometimes used to measure the twitch of muscle as it contracts in response to an electrical stimulus applied to a nerve. However, accurate measurement of the strength of amplitude of twitch, corresponding to the degree of neuromuscular block, is difficult: piezoelectric sensors (that accelerographs are based on) give variable results and can be masked by artifact from other movements. The visible response may disappear before full relaxation is achieved and the technique cannot be applied to smaller muscles on the face. The monitors demonstrate hysteresis, in that the measured values do not fully return to baseline values once blockade is reversed. Accelerometers also require full access to the muscle being monitored (usually the thumb), but the patients' arms may be unavailable to the anesthesiologist in a significant number of cases, as the patients' arms are often tucked under the surgical drapes. Mechanomyographs have fewer problems with hysteresis, but are difficult to place on the patient, are relatively bulky, they require access to the thumb for monitoring, and therefore cannot be used in surgical procedures that require a patient's arms to be tucked under the surgical drapes. Currently, there are no mechanomyographs available for purchase or for clinical use in the United States. The few remaining mechanomyographs were built in the 1990s and are used in a handful of research centers.

SUMMARY

[0013] Provided are systems, devices and methods for assessing muscle electrical activity in response to stimulation of a motor nerve. For example, the systems and method may be used while monitoring neuromuscular blockade of

muscles in patients being administered muscle relaxants. The muscle relaxant agent is optionally a neuromuscular blocking agent. Optionally, the muscle relaxant agent is a depolarizing agent. Optionally, the muscle relaxant agent is a non-depolarizing agent.

[0014] A method for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent according to one implementation of the invention can include stimulating a motor nerve to cause an evoked muscle response and recording the evoked muscle response. The evoked muscle response can be a floating differential signal. For example, the floating differential signal can be a non-ground-referenced differential signal. The method can further include quantifying the recorded muscle response and comparing the quantified muscle response to a control muscle response. The comparison indicates a level of neuromuscular blockade in the subject.

[0015] In some implementations, recording the evoked muscle response can include recording for muscle electrical activity in a muscle innervated by the motor nerve using two recording electrodes and determining a difference between the muscle electrical activity recorded by the each of the two recording electrodes. A difference between the muscle electrical activity recorded by each of the two recording electrodes can be accomplished without recording for muscle electrical activity using a common reference electrode. Alternatively or additionally, recording for muscle electrical activity in a muscle innervated by the motor nerve can be accomplished using no more than two recording electrodes.

[0016] Optionally, stimulating the motor nerve can include stimulating the motor nerve with a repeated train of temporally-spaced stimuli. For example, the motor nerve can be stimulated according to a train-of-four protocol or a tetanic protocol.

[0017] Additionally, the control muscle response can be a quantified muscle response caused by a prior or subsequent stimulus in the repeated train of temporally-spaced stimuli.

[0018] A system for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent according to one implementation of the invention can include a stimulator configured to generate one or more stimuli for stimulating a motor nerve to cause an evoked muscle response, a patient-stimulus interface configured to supply each stimulus generated by the stimulator to the patient and a patient-recording interface configured to record the evoked muscle response in a muscle innervated by the motor nerve. The evoked muscle response can be a floating differential signal. For example, the floating differential signal can be a non-ground-referenced differential signal. The system can also include at least one processing device configured to quantify the recorded muscle response and compare the quantified muscle response to a control muscle response. The comparison indicates a level of neuromuscular blockade in the subject.

[0019] Additionally, the patient-recording interface can include at least two recording electrodes for recording muscle electrical activity in the muscle innervated by the motor nerve. The non-ground-referenced differential signal can be a difference between the muscle electrical activity recorded by each of the at least two recording electrodes.

[0020] Optionally, the stimulator can be configured to stimulate the motor nerve with a repeated train of temporally-spaced stimuli. For example, the motor nerve can be stimulated according to a train-of-four protocol or a tetanic protocol.

[0021] Additionally, the control muscle response can be a quantified muscle response caused by a prior or subsequent stimulus in the repeated train of temporally-spaced stimuli.

[0022] A system for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent according to another implementation of the invention can include a stimulator configured to generate one or more stimuli for stimulating a motor nerve to cause an evoked muscle response, a patient-stimulus interface configured to supply each stimulus generated by the stimulator to the patient and a patient-recording interface including at least two recording electrodes. The patient-recording interface can be configured to record muscle electrical activity of a muscle innervated by the motor nerve. In addition, the patient-recording interface does not include a common reference electrode. The system can also include at least one processing device configured to quantify the recorded muscle response and compare the quantified muscle response to a control muscle response. The comparison indicates a level of neuromuscular blockade in the subject.

[0023] In addition, the recorded muscle electrical activity can be a floating differential signal. For example, the recorded muscle electrical activity can be a non-ground-referenced differential signal.

[0024] Optionally, the stimulator can be configured to stimulate the motor nerve with a repeated train of temporally-spaced stimuli. For example, the motor nerve can be stimulated according to a train-of-four protocol or a tetanic protocol.

[0025] Additionally, the control muscle response can be a quantified muscle response caused by a prior or subsequent stimulus in the repeated train of temporally-spaced stimuli.

[0026] An electrode system for use with a system for assessing neuromuscular blockade in a subject according to one implementation of the invention can include one or more stimulation electrodes configured to deliver a stimulus to a motor nerve of the subject and at least two recording electrodes configured to record muscle electrical activity of a muscle innervated by the motor nerve. The electrode system does not include a common reference electrode.

[0027] Additionally, the recorded muscle electrical activity is a difference between muscle electrical activity recorded by each of the at least two recording electrodes. For example, the recorded muscle electrical activity is a floating differential signal. Alternatively or additionally, the recorded muscle electrical activity is a non-ground-referenced differential signal.

[0028] A system for assessing muscle electrical activity in a subject according to yet another implementation of the invention may include: a motor nerve stimulator configured to stimulate a targeted motor nerve of the subject; a recording apparatus for recording electrical activity of a muscle innervated by the motor nerve; and a recording apparatus for recording electrical activity of the targeted motor nerve.

[0029] Optionally, the system may include at least one processor configured to identify whether an electrical response to the stimulus was recorded in the muscle.

[0030] Alternatively or additionally, the system may include at least one processor configured to identify whether an electrical response to the stimulus was recorded in the motor nerve.

[0031] In another implementation of the invention, the system may include a processing system configured to identify whether an electrical response to the stimulus was recorded in the muscle and whether an electrical response to the stimulus was recorded in the motor nerve.

[0032] For example, the processing system may be configured to indicate that the nerve was not stimulated if there is no electrical response to the stimulus recorded in the nerve.

[0033] In some implementations, the subject may have been administered a muscle relaxant agent.

[0034] According to other implementations, the processing system may be configured to indicate the presence of neuromuscular blockade in the subject when an electrical response to the stimulus is recorded in the nerve and there is an absent or diminished electrical response to the stimulus recorded in the muscle.

[0035] A method for identifying whether a motor nerve in a subject has been stimulated according to another implementation of the invention may include: applying a stimulus to the subject, wherein the stimulus is targeted to stimulate the motor nerve; recording for an electrical response to the applied stimulus in the targeted motor nerve; and recording for an electrical response to the applied stimulus in a muscle innervated by the targeted motor nerve. The presence or absence of an electrical response to the applied stimulus in the muscle and the presence or absence of an electrical response to the applied stimulus in the targeted motor nerve may be used to assess whether the motor nerve was simulated.

[0036] For example, the motor nerve may have been stimulated when an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the targeted motor nerve. However, the motor nerve may not have been stimulated when an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve, or when an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve.

[0037] In some implementations, the subject may have been administered a muscle relaxant agent prior to application of the stimulus to the subject. In this case, neuromuscular blockade in the subject may be indicated when an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve, or a diminished electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve.

[0038] A method for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent according to yet another implementation of the invention may include: applying a stimulus to the subject, wherein the stimulus is targeted to stimulate a motor nerve; recording for an electrical response to the applied stimulus in the targeted motor nerve; and recording for an electrical response to the applied stimulus in a muscle innervated by the targeted motor nerve. The recorded electrical response of the nerve and the recorded electrical response of the muscle may be used to assess neuromuscular blockade in the subject.

[0039] In this implementation, and similarly as discussed above, the motor nerve may have been stimulated when an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the targeted motor nerve. However, the motor nerve may not have been stimulated when an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve, or when an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve.

[0040] In addition, neuromuscular blockade in the subject may be indicated when an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve, or a diminished electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve.

[0041] Optionally, the method may also include determining an amplitude of the recorded electrical activity of the muscle. The determined amplitude compared to a control amplitude may indicate a level of neuromuscular blockade in the subject. In some implementations, the control amplitude may be an amplitude of recorded electrical activity of a prior or subsequent stimulus. Alternatively or additionally, the stimulus may be applied during application a train-of-four stimulus protocol.

[0042] A method for assessing neuromuscular blockage in a subject having been administered a muscle relaxant agent according to another implementation may include: applying a stimulus to the subject, wherein the stimulus is targeted to stimulate a motor nerve; recording for an electrical response to the stimulus in a muscle innervated by the targeted motor nerve; and recording for an electrical response to the stimulus in the targeted motor nerve. An absent or diminished electrical response to the stimulus in the muscle and the presence of an electrical response to the stimulus in the motor nerve may indicate neuromuscular blockade in the subject. In addition, the stimulus may be applied during application a train-of-four stimulus protocol to the subject.

[0043] A system for assessing muscle electrical activity in a subject according to another implementation may optionally include: a motor nerve stimulator configured to stimulate a targeted motor nerve of the subject; and a recording apparatus for recording electrical activity of a muscle innervated by the motor nerve and for recording electrical activity of the targeted motor nerve. The motor nerve stimulator may include its own power source and at least one stimulating electrode. In addition, the recording apparatus may include its own power source; and at least one recording electrode. Further, the motor nerve stimulator and the recording apparatus may be in galvanic isolation.

[0044] Optionally, the power source of the motor nerve stimulator and the power source of the recording apparatus may be dedicated power sources, each providing power to only the motor nerve stimulator or the recording apparatus, respectively.

[0045] Alternatively or additionally, the motor nerve stimulator may include no more than two stimulating electrodes, and the recording apparatus may include no more than two recording electrodes.

DESCRIPTION OF DRAWINGS

[0046] The components in the drawings are not necessarily to scale relative to each other. Like reference numerals designate corresponding parts throughout the several views.

[0047] FIG. **1** is a simplified block diagram illustrating a system for monitoring neuromuscular function during anesthesia;

[0048] FIG. **2** illustrates a flow diagram of example operations performed within the system of FIG. **1**;

[0049] FIG. **3** illustrates a flow diagram of example operations when placing electrodes;

[0050] FIG. **4** illustrates a flow diagram of example operations when determining a stimulation current and choosing a stimulation protocol;

[0051] FIG. **5** illustrates a flow diagram of example operations when monitoring neuromuscular block;

[0052] FIGS. **6**A-**6**F illustrate data collected in response to a nerve stimulus;

[0053] FIG. **7** illustrates a flow diagram of example operations when determining the validity of collected data;

[0054] FIG. **8** illustrates a flow diagram of example operations when applying the train-of-four (TOF) test protocol;

[0055] FIG. **9** illustrates a flow diagram of example operations when applying the tetanic test protocol;

[0056] FIG. **10** illustrates a flow diagram of example operations when applying the post-tetanic count (PTC) test protocol;

[0057] FIG. **11** illustrates a flow diagram of example operations when monitoring neuromuscular block during an example surgery;

[0058] FIG. **12** illustrates a flow diagram of example operations when performing the TOF test protocol prior to intubation;

[0059] FIG. **13** illustrates a flow diagram of example operations when performing the tetanic test protocol during surgery and the TOF test protocol after administering reversal drugs;

[0060] FIG. **14** illustrates a flow diagram of example operations when turning off the monitoring device;

[0061] FIG. **15** illustrates a flow diagram of example operations when removing electrodes; and

[0062] FIG. **16** illustrates an example processing device.

DETAILED DESCRIPTION

[0063] Provided are systems, devices and methods for monitoring anesthesia. For example, the methods, devices and systems are optionally used to assess neuromuscular blockade in a subject who has received a muscle relaxant agent. The muscle relaxant agent is optionally a neuromuscular blocking agent. Optionally, the muscle relaxant agent is a depolarizing agent. Optionally, the muscle relaxant agent is a non-depolarizing agent.

[0064] The disclosed systems, devices and methods provide an objective measure of nerve and muscle function that corresponds directly to effects that the muscle relaxant agent has on the body. Relaxants can thus be more effectively administered and reversed, providing more precise control over induction of anesthesia and relaxation, and identifying when surgical procedures can be started safely. Periodic muscle function monitoring can also guide the titration of muscle relaxants during the surgery to avoid over- and under-dosing, and can signal when a patient has adequately responded so that the endotracheal (breathing) tube can be introduced (at the beginning of the surgical procedure) or withdrawn (at the end of surgical procedure).

[0065] The systems, devices and methods are optionally used to objectively measure the depth of neuromuscular blockade accurately and continuously throughout surgical procedures. The neuromuscular function is directly assessed by comparing the evoked muscle response (the evoked electrical activity behind the muscle "twitch") in response to electrical stimulation of the corresponding motor nerve. Adequate muscle relaxation has been achieved when the muscle response to repetitive stimulation is extinguished while nerve conduction remains intact. The device repeats the assessment when manually or automatically triggered (at user-selected intervals), providing ongoing monitoring of neuromuscular function status throughout any procedure, using any peripheral motor nerve. Battery-powered, easily applied, clearly visible and shaped to integrate comfortably into the operative setting, the device is the reliable objective monitor that assures controlled drug delivery and appropriate return of neuromuscular function to ensure appropriate surgical conditions thus improving patient safety.

[0066] As discussed above, muscle relaxants are administered during some types of surgeries. Muscle relaxants interrupt the chemical conduction across the neuromuscular junction, but do not affect the electrical conduction in either the nerve or the muscle fibers. In particular, the muscle relaxants block receptor sites, which prevent chemical messengers from initiating an electrical response in the muscle fiber. As more receptor sites are blocked, fewer muscle fibers receive stimulation, and both the visible mechanical twitch and the underlying electrical response in the muscle decrease. A single administration of muscle relaxants causes a rapid decrease in the response of the muscle, which then restores to normal over time as the drug is metabolized and then excreted by the body (spontaneous recovery). The magnitude of decrease of the muscle response depends on both the time since drug administration and the muscle involved. For example, the thumb muscle is affected to a greater degree for the same dose of muscle relaxants than the diaphragm. Successful monitoring, therefore, depends both on identifying the correct muscle, and on continuous monitoring of the evolving effect of muscle relaxant administration and withdrawal (reversal).

[0067] Prior to administering the muscle relaxants to the patient, a nerve impulse evoked by the stimulation travels to the muscle and elicits both an electrical response and a muscle twitch. As the muscle relaxants are applied, the receptor sites are blocked and only some muscle fibers respond. Thus, although the nerve response remains unchanged in strength, the amplitude of the muscle response diminishes, an effect more pronounced in the twitch than in the electrical recording. At full block, all muscle responses are abolished, but the nerve response is preserved. Thus, it is possible to detect a procedural error in the case where the stimulus is moved distant to the nerve, because in such a case, there will be no detected nerve or muscle response.

[0068] Referring to FIG. **1**, a system used to assess the depth of muscle paralysis and degree of muscle recovery in patients receiving muscle relaxants during surgical procedures is described. The system may consist of a stimulating/recording unit **130** and a control/visualization unit **132**. The stimulating/recording unit **130** and the control/visualization unit **132** may be connected by a cable or a wireless link. Additionally or alternatively, the stimulating/recording unit **130** and the control/visualization unit **132** may be combined into a single package. However, the effect of electrical noise (i.e., electrocautery) and the physical inconvenience of having additional wires alongside the patient can be minimized if the stimulating/recording unit **130** and the control/visualiza-

tion unit **132** are physically separated. When physically separated, the stimulating/recording unit **130** and the control/visualization unit **132** may be separate, single, hand-held packages. In addition, the control/visualization unit **132** may be lightweight, textured along the edges but without sharp corners or projecting surfaces. The control/visualization unit **132** may be capable of sitting on a flat surface or being attached to an IV pole and may be constructed of materials with colors that fit operating room standards (i.e., blue and silver). In addition, the control/visualization unit **132** may be amenable to cleaning and sterilization with a damp cloth or alcohol wipe. The control/visualization unit **132** may also be capable of surviving repeated drops from approximately four feet onto a hard floor. In some implementations, the control/visualization unit **132** may be a laptop, a tablet computer, and may be battery operated, and of a medical grade type.

[0069] The stimulating/recording unit **130** may include a nerve stimulator **108** and sensors **110** and **112**, which may optionally be integrated into a single, hand-held package. The nerve stimulator **108** is capable of delivering electrical pulses to a motor nerve such as the median or ulnar nerve at the wrist, the tibial nerve at the ankle or the facial nerve beneath the ear, for example. In one implementation, the nerve stimulator **108** may deliver a 200 μs or 300 μs square-wave, monophasic, constant electrical pulse. The electrical pulse delivered by the nerve stimulator **108** should be sufficient in strength to elicit nerve responses when the patient is in an unblocked state. In addition, the nerve stimulator **108** may be capable of delivering sequences of pulses, for example train-of-four (TOF) and tetanic bursts.

[0070] The sensors **110** and **112** are capable of sensing the intrinsic electrical activity of the nerve and muscle, which are induced by the nerve stimulation. By sensing the electrical activity of the muscle, for example, it is possible to measure the amplitude of the electrical activity, which directly corresponds to the strength of the muscle response. Accordingly, it is possible to determine the impact that the muscle relaxants have on the patient at any point in time during the surgery because changes in the amplitude of the electrical activity of the muscle can be correlated directly to changes caused by addition and reversal of the muscle relaxants.

[0071] Stimulating electrodes **102** and sensing electrodes **104** and **106** may be attached to the stimulating/recording unit **130** using a custom connector, for example. The system shown in FIG. **1** may also include a power regulator **114** that supplies power to both the stimulating/recording unit **130** and the control/visualization unit **132**. In some implementations, however, the stimulating/recording unit **130** and the control/visualization unit **132** may be separately powered (i.e., by two separate battery packs). The stimulating/recording unit **130** and the control/visualization unit **132** may be isolated from each other using a galvanic separator **116**, for example, to prevent direct current from flowing between the stimulating/recording unit **130** and the control/visualization unit **132**. In addition, the nerve stimulator **108** may optionally receive power from a dedicated power source (i.e., a battery) that is not utilized by other units, such as the sensors **110** and **112** utilized for recording electrical activity of the muscle and nerve. Similarly, the sensors **110** and **112** utilized for recording electrical activity of the muscle and nerve may optionally receive power from a dedicated power source (i.e., a battery) that is not utilized by other units, such as the nerve stimulator **108**. In this implementation, there is no galvanic connection between the nerve stimulator **108** and the sensors **110** and **112**, and the nerve stimulator and sensors may communicate via galvanic isolated modules with a controller on which the program modules run (i.e., the control/visualization unit **132**). Accordingly, the sensors **110** and **112** may operate in a floating setting, thus eliminating the need for a reference electrode in addition to the bipolar electrodes which sense the electrical activity. For example, the sensor **110** can include two recording electrodes (e.g., sensing electrodes **104**) and can be configured to record the electrical activity of the muscle innervated by the stimulated motor nerve. The sensor **110** does not need to include a common reference electrode. The recorded electrical activity can be a floating differential signal. For example, the recorded electrical activity can be a non-ground-referenced differential signal. In other words, the difference between the electrical activity recorded by each of the sensing electrodes **104** can be obtained without recording for electrical activity using a common reference electrode. Optionally, the sensor **112** can include two recording electrodes (e.g., sensing electrodes **106**) and can be configured to record the electrical activity of the stimulated motor nerve. Similarly to sensor **110**, the sensor **112** does not need to include a common reference electrode. Thus, the motor nerve may be stimulated and the electrical activity of the muscle or nerve may be measured using four wires (i.e., two for stimulation and two for recording) without the need for a fifth wire used in related devices, for example for a ground, which simplifies system setup and minimizes the cost of the electrode array. For example, an electrode system of the stimulating/recording unit **130** can include two stimulating electrodes (i.e., stimulating electrodes **102**) and two recording electrodes (e.g., sensing electrodes **104**) for recording the electrical activity of the muscle innervated by the stimulated motor nerve, i.e., a four-electrode configuration. Eliminating the common reference electrode simplifies system set up because only four electrodes, not five electrodes, need to be placed on the patient. Additionally, the chance of failure due to electrode disconnection from the patient's skin is reduced because there are fewer electrodes. Further, with fewer recording electrodes, the electrode system can be made smaller, which is a benefit for pediatric and neonatal applications, and at a lower cost. Optionally, the electrode system of the stimulating/recording unit **130** can include two recording electrodes (e.g., sensing electrodes **106**) for recording the electrical activity of the stimulated motor nerve. As discussed above, the electrode system does not need to include a common reference electrode.

[0072] In related systems, stimulation and recording circuits are connected to a common ground (e.g., earth-ground systems). Because the stimulation and recording circuits are connected to a common ground, current loops are created, which leads to cross-talk between the stimulation and recording circuits. Recording channels can therefore include stimulus artifact, which obscures the electrical activity of the muscle or nerve response. As discussed in detail below, the neuromuscular monitoring systems and methods described herein rely on the relative difference between two features of the recorded electrical activity (e.g., peak-to-peak, peak-to-baseline, etc.), and not on the absolute value. Accordingly, a common reference point such as earth-ground, for example, is not necessary. As discussed above, the stimulation/recording unit **130** can be battery-powered, and therefore, the connection to earth-ground can be eliminated. This enhances patient safety by eliminating electrical paths that can conduct stray currents present in the patient through the stimulation/

recording unit **130** to earth ground. This also reduces shock hazards and eliminates the possibility of leakage currents that can cause cardiac arrhythmia.

[0073] The control/visualization unit **132** may contain user-input controls and a visual display, store operating protocols, collect patient data and generate a system clock. For example, the control/visualization unit **132** may include input and output devices **118**, a processing device **120**, an IV-pole holder **122** and an external communication link **124**. The input and output devices **118** may include user-input controls such as, for example, a power on/off control, a test protocol selection control (single twitch, Train of Four (TOF), tetanic, Post-tetanic count (PTC)), a stimulus intensity control (0-100 mA constant current), a stimulus mode control (manual or continuous), a stimulus trigger control, etc. The user-input controls may consist of backlit buttons for indicating active modes and successful selections, and audible tones may optionally be used for alarms. In addition, the user-input controls may be designed such that the user can operate the controls while wearing surgical gloves.

[0074] The input and output devices **118** may include a display. For example, the display may be capable of displaying a visual indicator that the control/visualization unit **132** is on, fault indicators (i.e., low battery, loss of electric continuity, failure to deliver stimulus, loss of communication connection), stimulus intensity, bar graphs representing responses to the stimuli, etc. The display is not limited to the visual indicators listed above, and instead may consist of a number of combinations of visual indicators that allow the user to more easily operate the system. The system shown in FIG. **1** may also include a processing device **120** for implementing aspects described herein. An example processing device is discussed in detail below with regard to FIG. **16**.

[0075] In addition, the system shown in FIG. **1** may include an IV-pole holder **122** and an external communication link **124**. The IV-pole holder **122** may be used for securing the control/visualization unit **132** to the IV pole during the surgery. The external communication link **124** allows the system to communicate with other devices. At the conclusion of the surgery, it may be possible to download the collected data from the control/visualization unit **132** using the external communication link **124**.

[0076] FIG. **2** illustrates a flow diagram of example operations performed within the system of FIG. **1**. The example operations of FIG. **2** may be performed during surgery, for example. The example operations of FIG. **2** are divided into four phases, i.e., Preparation, Stimulation, Interpretation and Clean-up. During the preparation phase, the patient is admitted into the operating room. Then, at **202**, the electrodes are placed on the patient. The electrodes may be, for example, the stimulation electrodes **102** and the sensor electrodes **104** and **106**, as shown in FIG. **1**. The process of placing the electrodes on the patient is discussed in detail with regard to FIG. **3**.

[0077] After placing the electrodes on the patient, general anesthesia may be administered to the patient. Next, at **204**, the anesthesiologist may choose the stimulation current (i.e., stimulus intensity) and the stimulation protocol to be used while monitoring the neuromuscular block. Although, the term anesthesiologist is used throughout one skilled in the art will appreciate the system can be operated by other medical professionals or system operators and that the use of the term anesthesiologist does not limit the scope of the disclosed devices and methods. The anesthesiologist may choose the stimulation current either manually or automatically, which is discussed in detail with regard to FIG. **4**. In addition, the anesthesiologist may choose from a number of stimulation protocols including but not limited to single twitch, TOF, tetanic and PTC. The process of choosing a stimulation protocol is discussed in detail with regard to FIG. **4**, and the particular stimulation protocols are discussed in detail with regard to FIGS. **8-10**.

[0078] After choosing both the stimulation intensity and protocol, the anesthesiologist may begin to administer the muscle relaxant, which induces the neuromuscular block. In order to monitor anesthesia levels during the surgery, at **206**, the anesthesiologist may monitor the neuromuscular block. The process of monitoring the neuromuscular block is discussed in detail with regard to FIGS. **5-11**. Then, after the patient has adequately regained neuromuscular function at the conclusion of the surgery, the anesthesiologist may stop applying stimuli, save data and/or parameters, turn off the device and remove the electrodes from the patient at **208**. This process is discussed in detail with regard to FIGS. **14** and **15**.

[0079] FIG. **3** illustrates a flow diagram of example operations when placing electrodes. At **302**, the anesthesiologist determines the nerves and muscles to stimulate and/or record. First, the anesthesiologist may choose the nerve to stimulate. For example, the anesthesiologist may choose to stimulate a motor nerve, which extends to the surface of a muscle where it contacts at the neuromuscular junction, such as the median or ulnar nerve at the wrist, the tibial nerve at the ankle, the facial nerve beneath the ear, etc. The evoked muscle responses may be recorded at the motor units innervated by the stimulated nerve. In addition, the evoked nerve responses may be recorded along the nerve pathway to either side of the stimulating site.

[0080] At **304**, the anesthesiologist may connect the stimulating electrodes **102** and the sensor electrodes **104** and **106** to wires attached to the stimulating/recording unit **130**. As discussed above, the stimulating and sensor electrodes **102**, **104** and **106** may be attached to the stimulating/recording unit **130** through a custom connector.

[0081] At **306**, the anesthesiologist may locate the nerves and muscles for stimulating and recording. As discussed above, the anesthesiologist may choose to stimulate a motor nerve such as the median or ulnar nerve at the wrist, the tibial nerve at the ankle, the facial nerve beneath the ear, etc. In order to record the evoked muscle responses, the anesthesiologist may locate the motor units that will be innervated by the stimulated nerve, such as the hand for the ulnar nerve, the foot for the tibial nerve or the eyebrow or jaw for the facial nerve. Then, the anesthesiologist may locate the nerve from which to record the evoked nerve response. The evoked nerve response may be recorded along the nerve pathway to either side of the stimulating site, but should preferably be recorded at least 5 cm away from the stimulating site to avoid interference. In one implementation, differential recording leads may be placed over active sites, i.e., one lead over the muscle and the other lead over the nerve to collect both responses in a single recording channel.

[0082] At **308**, the anesthesiologist may place the stimulating electrodes **102** over the nerve to be stimulated and the sensing electrodes **104** and **106** over the motor units innervated by the stimulated nerve and along the nerve pathway, respectively.

[0083] FIG. **4** illustrates a flow diagram of example operations when determining a stimulation current and choosing a stimulation protocol. At **402**, the anesthesiologist may deter-

mine the stimulation current (i.e., stimulation intensity) using, for example, the user-input controls of the control/visualization unit **132**. The anesthesiologist may choose the stimulation intensity either manually or automatically. When choosing the stimulation intensity manually, the anesthesiologist may choose the actual stimulation current, for example, between 0-100 mA. In addition, the anesthesiologist may manually choose either the supra-maximal or submaximal current by increasing/decreasing the current in a predetermined sequence of incremental current changes in, for example 5 mA increments, until achieving maximal EMG+10% response (supramaximal) or threshold EMG+10% response (submaximal), respectively. Further, the anesthesiologist may choose the stimulation intensity automatically, which sets either the supra-maximal or submaximal current by applying the predetermined sequence of incremental current changes automatically until the maximal EMG+10% response or the threshold EMG+10% response is obtained. The system may also include a default stimulation intensity, i.e., supra-maximal, in the event that the anesthesiologist does not choose a stimulation intensity.

[0084] At **404**, the anesthesiologist may choose the stimulation protocol. For example, the anesthesiologist may choose among single twitch, TOF, tetanic and PTC protocols using, for example, the user-input controls of the control/visualization unit **132**. For the single twitch protocol, a single electrical pulse is applied, and the corresponding muscle response is recorded. For example, a single electrical pulse at supra-maximal intensity level may be applied for 200 μs, and the evoked muscle response may be recorded. The single electrical pulses of 200 or 300 μs duration may be repeated every 1 or every 10 seconds in a 1/sec (1 Hz) protocol or 1/10 sec (0.1 Hz) protocol.

[0085] For the TOF protocol, a predetermined pattern of stimuli may be applied at predetermined intervals. For example, a pattern of four electrical pulses each at supra-maximal intensity level for 200 μs or 300 μs may be applied every 500 ms. Each applied stimulus evokes a corresponding muscle response, which is recorded. Then, a ratio of the amplitude of a subsequent muscle response to the amplitude of a prior muscle response is calculated. For example, the ratio of the fourth muscle response to the first muscle response may be calculated (TOF ratio). In mild neuromuscular block, the evoked muscle responses progressively decrease in amplitude from the first to the fourth stimulus. Thus, by calculating the TOF ratio, it may be possible to determine the level of neuromuscular block because the TOF ratio corresponds to the level of neuromuscular block.

[0086] For the tetanic (TET) protocol, a predetermined pattern of stimuli may be applied at predetermined intervals similarly to the TOF protocol. However, in TET, a larger number of stimuli are applied at a higher frequency (i.e., 50 Hz, 70 Hz or 100 Hz) and for a longer total duration (i.e., 5 sec). The frequency used for the TET protocol may preferably be above a threshold frequency that achieves fusion of the muscular response to the stimulation, such as greater than 30 Hz in humans, for example. For example, a pattern of 250 or 500 electrical pulses (each of 200 μsec duration), and each at supra-maximal (or less than supramaximal) intensity level at a rate of 50 or 100 Hz for five seconds may be applied. During normal neuromuscular transmission, the evoked muscle responses to the tetanic stimulation fuse into a single sustained contraction of the muscle. In other words, the normal (unblocked) muscle response to the tetanic stimulation is sustained for the duration of the stimulation. However, during a non-depolarizing neuromuscular block, the response to the tetanic stimulation will not be sustained (i.e., fade occurs). Thus, it may be possible to determine the level of neuromuscular block by calculating the ratio of the amplitude of the muscle response at the end of the stimulation to the amplitude of the muscle response at the beginning of the stimulation.

[0087] For the PTC protocol, a tetanic stimulation may be applied as discussed above. After the end of the tetanic stimulation, single twitch stimuli may be applied at predetermined intervals. For example, single-twitch stimuli may be applied at a rate of 1 Hz beginning 30 seconds after the end of the tetanic stimulation, and the number of responses to the single-twitch stimuli may be counted. The tetanic stimulation causes release of all available neurotransmitter from the nerve terminal, which may restore twitch response for a short interval following the tetanic stimulation. During deep neuromuscular block, the time until return of the first response to TOF stimulation is related to the number of PTC twitch responses present at a given time.

[0088] In addition to choosing a stimulation protocol, the anesthesiologist may also choose whether the stimulation will be continuous or manual. For manual stimulation, the anesthesiologist may trigger application of the stimuli using the user-input controls of the control/visualization unit **132**. For continuous stimulation, successive stimulation protocols may be applied at predetermined time intervals. Single twitch, TOF, tetanic and PTC protocols may be repeated every 1 second, 12 seconds, 120 seconds and 120 seconds, respectively, for example.

[0089] FIG. **5** illustrates a flow diagram of example operations when monitoring neuromuscular block. At **502**, the anesthesiologist may apply stimuli according to the chosen protocol. At **504**, the muscle response is sensed and recorded using the sensing electrodes **104**, and at **506**, the nerve response is sensed and recorded using the sensing electrodes **106**. At **508**, a determination is made as to whether the collected data are valid. This is discussed in detail with regard to FIG. **7**. At **510**, a subsequent stimulus may be applied after a predetermined period of time has elapsed since the previous stimulus, which is determined at **512**.

[0090] FIGS. **6**A-**6**F illustrate data collected in response to a nerve stimulus. In order to measure the nerve and muscle responses, the systems and methods disclosed herein begin with an epoch of collected data in response to a stimulus. For example, FIG. **6**A illustrates data collected (i.e., a detected voltage signal) by the sensors **104** and **106** in response to the applied stimulus. The collected data include noise (the stimulus artifact), the electrical activity of the nerve (i.e., the nerve response) and the electrical activity of the muscle (i.e., the muscle response). In one implementation, the noise, nerve response and muscle response may be separated from one another before each is measured.

[0091] First, the limits of the neuromuscular activity may be detected by identifying the point where the detected voltage signal deviates significantly from the baseline value [i.e., the background (pre-stimulus or immediately post-response) level of electrical activity (characterized by, for example, the Root Mean Square (RMS) amplitude)], for example, by working inward from the high- and low-ends of the sequence of values making up the detected voltage signal. Then, when both the slope and amplitude differ by a predetermined amount from their respective baseline values, a limit may be declared and a fiducial mark **602** may be placed to indicate the

location. The point where both the slope and amplitude differ by a predetermined amount from their respective baseline values may be visually identified by a "knee" in the detected voltage signal. The "knee" and fiducial mark **602** are shown in FIG. **6**B, which illustrates a portion of FIG. **6**A. The portions of the detected voltage signal that precede and follow the fiducial marks **602** as shown in FIG. **6**C are noise-only segments that can be assessed for artifact and unacceptable levels of interference. The portion of the detected voltage signal between the fiducial marks **602** is the neuromuscular response, which contains both the nerve and muscle responses and noise.

[0092] The region of the detected voltage signal shown in FIG. **6**C and marked "Signal" may be further subdivided into the respective nerve and muscle responses contained in the detected voltage signal by a number of means. First, the muscle response **606** generally occurs later in time (and is of higher amplitude) than the nerve response **604** because the muscle activates after the nerve. Thus, it may be possible to identify and then subtract the muscle response **606** from the detected voltage signal to obtain the nerve response **604**. Second, the constant portions of the detected voltage signal are presumed to belong to the nerve response **604** because the muscle response **606** is more variable than the nerve response **604**, which is constant over time when present, and therefore, the nerve response **604** can be identified and then subtracted from the detected voltage signal to obtain the muscle response **606**. Third, the muscle response **606** has a characteristic shape that may be fitted to and then subtracted from the detected voltage signal to obtain the nerve response **604**. The noise **608**, nerve response **604** and the muscle response **606** are shown separately in FIGS. **6**D, **6**E and **6**F, respectively.

[0093] After the three portions of the detected voltage signal (i.e., noise **608**, nerve response **604** and muscle response **606**) have been separated, each respective portion may be measured. The noise **608** may be analyzed to determine whether artifact is present. Additionally or alternatively, the noise **608** may be statistically analyzed, the slope and/or RMS value across the region may be calculated or the frequency content may be estimated by counting zero crossings. The nerve response **604** may be assessed for consistency, for example by determining whether the nerve response **604** changes shape or amplitude. The nerve response **604** is expected to be consistent, or not changing in shape or amplitude. The nerve response **604** may also be assessed by analyzing the amplitude and intervals between major features, or performing correlation checks of the aligned detected voltage signal and a template composed from prior recordings. However, in some cases, it may be difficult to distinguish the nerve response from background electrical noise because the amplitude of the nerve response is relatively small as compared to the amplitude of the muscle response to the same stimulus. Optionally, a plurality of nerve responses to a plurality of applied stimuli may be averaged in order to record the nerve response. In this regard, the term stimulus, as used, for example, in the description of an applied or applying a stimulus optionally includes one or more individual stimuli. The muscle response **606** may be assessed by measuring the peak-to-peak amplitude, the baseline-to-peak amplitude or the difference between peak values.

[0094] FIG. **7** illustrates a flow diagram of example operations when determining validity of collected data. Prior to analyzing the collected data, a determination is made as to whether the collected data are valid. The validity determination begins at **702**. For example, electrode connection integrity, temperature, noise levels, etc. may be analyzed. At **704**, a determination is made as to whether the electrode connection is sufficient. For example, the electrode connection may be sufficient if the impedance is between 500 and 5,000 Ohms. At **706**, a determination is made as to whether the temperature is sufficient. When temperature is insufficient (i.e., too low), nerve function may be impaired by the low temperature. Thus, low temperature may be detected, and the area may be heated to normal body temperature in order to eliminate the possibility of errors. In some implementations, temperature of the skin may be detected in order to estimate temperature of the nerve because the temperatures will be approximately the same at any given time. For example, the temperature may be sufficient if it is greater than or equal to 34° C. At **708**, a determination is made as to whether the signal-to-noise ratio (SNR) is sufficient. In one implementation, the electrode connection, temperature and signal-to-noise ratio must all be sufficient to proceed. In other implementations, the above condition may not be required. If conditions are insufficient, then the user may be notified at **710** so that the insufficient condition may be remedied, and the validity checks may be repeated. As discussed above, the insufficient condition may be displayed on the control/visualization unit **132**.

[0095] At **712**, a determination is made as to whether the stimulus was delivered. When the stimulus is moved off of (i.e., distant from) the motor nerve and the stimulus is thus unable to trigger a nerve response, both the muscle response and the nerve response, as sensed by the sensing electrodes **104** and **106**, will be non-existent. For example, the stimulus may be applied to target a motor nerve such as the median, ulnar, tibial or facial nerve. As discussed above, stimulating electrodes are placed on the patient in proximity to the targeted motor nerve. By targeting a specific motor nerve, a muscle response at the muscle innervated by the targeted nerve is expected. However, it is difficult to visually determine if the stimulating electrodes have been placed such that the stimulus will actually be delivered to the targeted motor nerve. In some cases, grossly misplaced electrodes may directly stimulate the muscle rather than the nerve, failing to assess conduction across the neuromuscular junction as intended. In addition, after muscle relaxants are administered, a muscle response at the muscle innervated by the targeted nerve decreases or diminishes (i.e., is less than the expected response without muscle relaxants) to zero in relation to the amount of administered muscle relaxants. Accordingly, if the stimulating electrodes are placed distant from the targeted motor nerve, the stimulus will not actually be delivered to the targeted motor nerve. In this case, it may be difficult to determine whether the stimulus was delivered by recording electrical activity of the muscle alone because the muscle response diminishes to zero as muscle relaxants are administered. According to some implementation of the invention, it may be possible to assess whether the stimulus has been delivered to the targeted motor nerve by recording for electrical activity of the stimulated motor nerve because electrical activity of the stimulated motor nerve is always present if the stimulus is delivered to the targeted motor nerve.

[0096] The nerve response should be present even during full neuromuscular block. Thus, if the nerve response is non-existent, then the stimulus was not delivered (or the stimulus was not sufficient to trigger a nerve response). In addition, it may be possible to detect whether the stimulus was delivered

by detecting some twitch based on motion artifacts appearing in the impedance channel. If the stimulus was not delivered, the user may be notified, and the validity checks may be repeated at **716**. As discussed above, the insufficient condition may be displayed on the control/visualization unit **132**.

[0097] At **714**, a determination is made as to whether the response is valid. For example, the nerve and muscle responses may be analyzed to determine whether each response is present, the amplitudes are decreasing, the response latency is consistent, etc. If the response is invalid, the user may be notified, and the validity checks may be repeated at **716**. As discussed above, the insufficient condition may be displayed on the control/visualization unit **132**. After determining that the collected data are valid, it is possible to proceed with the stimulation at **718** and measure the amplitude of the muscle response.

[0098] FIG. **8** illustrates a flow diagram of example operations when applying the TOF protocol. The TOF protocol consists of applying a predetermined pattern of stimuli at predetermined intervals to the motor nerve. At **802**, the TOF protocol begins, and at **804** the first stimulus is applied. For example, the stimulus may be a 200 μs or 300 μs, square-wave, monophasic, constant current electrical pulse. As discussed above, the control/visualization unit **132** may indicate that the stimulus has been applied, for example using an indicating light. At **806**, the nerve and muscle responses are recorded by the sensing electrodes **104** and **106**. Thereafter, at **808**, a determination is made as to whether a predetermined number of stimuli have been applied. In one implementation, the predetermined number is preferably four stimuli, but it may also be five, six, seven, etc. If Yes, at **812**, a determination is made as to whether the collected data are valid, which is discussed in detail with regard to FIG. **7**. If No, a subsequent stimulus is applied after a predetermined time interval, for example 500 ms, has elapsed. However, the predetermined time interval may be greater or less than 500 ms.

[0099] At **814**, the amplitude of the muscle response is measured. As discussed above, the amplitude may be the peak-to-peak or the baseline-to-peak amplitude. The measured amplitude may be compared to a control amplitude to determine the level of neuromuscular block. For example, the control amplitude may be zero. When the predetermined pattern of stimuli is applied to the patient before administration of the muscle relaxants, the amplitude of the muscle responses are expected to be approximately equal and non-zero. However, as muscle relaxants are administered to the patient, the amplitude of each subsequent muscle response diminishes. In one implementation, the amplitude decreases to zero, preferably by the fourth recorded muscle response, which may indicate a certain degree of neuromuscular block.

[0100] At **816**, the TOF ratio may be determined by calculating a ratio of amplitudes of any two, distinct muscle responses to a train of sequentially applied stimuli. In some implementations, the ratio may be a ratio of the amplitude of a subsequent muscle response (i.e., recorded later in time) to the amplitude of a previous muscle response (i.e., recorded earlier in time). For example, the train-of-four ratio is the ratio of the amplitude of the fourth sequentially applied stimulus to the first sequentially applied stimulus in a train of sequentially applied stimuli. The TOF ratio may then be compared to a control ratio (which should preferably be 1.0). Preferably, the TOF ratio will be a ratio of the amplitude of the fourth muscle response to the amplitude of the first muscle response, but can alternatively be the ratio of the amplitudes of any of the first, second, third, fourth, fifth, six, etc. muscle responses. In an unblocked state, the TOF ratio is approximately 1.0. As the neuromuscular block deepens, the TOF ratio falls progressively to 0.0. Thus, a smaller TOF ratio, i.e., one that approaches 0.0, corresponds to a greater level of neuromuscular block, and a TOF ratio of the fourth to the first muscle response of 0.0 indicates approximately greater than or equal to 80% neuromuscular block.

[0101] Next, a determination is made as to whether the TOF ratio equals zero. If No, the control/visualization unit **132** may display the TOF ratio value, as well as a corresponding color. The display may utilize different colors to indicate different levels of neuromuscular block. For example, the color green may be used to represent a TOF ratio between 1.0 and 0.90, the color yellow may be used to represent a TOF ratio between 0.89 and 0.40 and the color red may be used to represent a TOF ratio between 0.39 and 0.01. If Yes, at **818**, the TOF count is calculated. For example, when the TOF ratio is 0.0 (i.e., the fourth muscle response is non-existent), a determination is made as to how many stimuli (i.e., first, second and third stimuli) exhibited a non-zero response. As neuromuscular block deepens, the TOF count decreases from three counts to zero. For example, when the TOF ratio is 0.0 and the TOF count is zero, the neuromuscular block is approximately greater than or equal to 95%. In contrast, as neuromuscular block lessens, the TOF count increases. When the TOF ratio is 0.9 (and the TOF count is, by definition, four), the neuromuscular block is approximately less than or equal to 70%. This level of neuromuscular function (less than 70% block) is considered the threshold for adequate recovery. The TOF count value may then be displayed on the control/visualization unit **132**, along with a corresponding color. In other implementations, the TOF count may be calculated for greater than four applied stimuli.

[0102] At **820**, a determination is made as to whether the stimulation mode is manual or continuous. When the stimulation mode is manual, a subsequent stimulation protocol is applied only after the user triggers application using for example, user-input controls of the control/visualization unit **132**. When the stimulation mode is continuous, at **822**, a determination is made as to whether a predetermined time between stimulation protocols has elapsed. Preferably, the predetermined sequential time for the TOF protocol is 12 seconds. In addition, the control/visualization unit **132** may display the time remaining until application of the next stimulation protocol.

[0103] FIG. **9** illustrates a flow diagram of example operations when applying the tetanic test protocol. Similarly to the TOF protocol, the tetanic protocol consists of a predetermined pattern of stimuli applied at predetermined intervals. Unlike the TOF protocol, however, the tetanic protocol consists of applying a larger number of stimuli at a higher frequency. At **902**, application of the stimuli begins, and at **904**, the first stimulus is applied. For example, 250 or 500 electrical pulses may be applied at a rate of 50 or 100 Hz in a five-second period. In addition, each stimulus (electrical pulse) may have a duration of 200 μs. Application of the stimulus may be displayed at the control/visualization unit **132** using an indicating light and/or a sound, for example. At **906**, the nerve and muscle responses are recorded by the sensing electrodes **104** and **106**. Thereafter, at **908**, a determination is made as to whether a predetermined number of stimuli (i.e., 250 or 500) have been applied. If Yes, at **912**, a determination is made as to whether the collected data are

valid, which is discussed in detail with regard to FIG. **7**. If No, a subsequent stimulus is applied after a predetermined time interval, for example 4 ms or 2 ms, when the pulses are applied at a rate of 50 or 100 Hz, respectively, has elapsed at **910**.

[0104] At **914**, the amplitude of the muscle responses is measured, and at **916**, the tetanic ratio is calculated. Similarly to the TOF ratio, the tetanic ratio may be the ratio of an amplitude of a subsequently applied stimulus to an amplitude of a previously applied stimulus, i.e., the last stimulus to the first stimulus in the train of stimuli. However, as discussed above, the ratio may be the ratio of amplitudes of any two, distinct muscle responses to a train of sequentially applied stimuli. As the neuromuscular block deepens, the tetanic ratio falls progressively from a normal baseline of 1.0 towards 0.0. Thus, a smaller tetanic ratio, i.e., one that approaches 0.0, corresponds to a greater level of neuromuscular block. If the tetanic ratio equals zero, at **918**, the tetanic duration may be calculated. The tetanic duration may be calculated by estimating the duration of the time interval between the non-zero start and the end of the response, i.e., 0-4.9 seconds. As discussed above, during normal neuromuscular transmission, the evoked muscle responses to the tetanic stimulation merge into a single sustained contraction of the muscle. However, during neuromuscular block, the amplitude of responses to the tetanic stimulation will not be sustained (i.e., fade occurs). Accordingly, the level of neuromuscular block may correspond to the time interval of the response. In addition, the tetanic duration value may be displayed by the control/visualization unit **132**, along with the corresponding color.

[0105] At **920**, a determination is made as to whether the stimulation mode is manual or continuous. When the stimulation mode is manual, a subsequent stimulation protocol is applied only after the user triggers application using for example, user-input controls of the control/visualization unit **132**. When the stimulation mode is continuous, at **922**, a determination is made as to whether a predetermined time between stimulation protocols has elapsed. Preferably, the predetermined time for tetanic protocol is 120 seconds (i.e., the duration elapsed between successive tetanic stimulations is at least 120 sec in order to avoid the phenomenon of "post-tetanic potentiation" which would invalidate the neuromuscular responses). In addition, the control/visualization unit **132** may display the time interval until application of the next stimulation protocol.

[0106] FIG. **10** illustrates a flow diagram of example operations when applying the post-tetanic count (PTC) test protocol. When a deep neuromuscular block is achieved, and estimation using either the TOF protocol or the tetanic protocol is not elicited, it may be possible to elicit a response using a special stimulus protocol, i.e., the PTC protocol. At **1002**, the stimulation protocol begins, and at **1004**, the first stimulus is applied. Preferably, the first stimulus is a tetanic stimulation, or a pattern of 250 or 500 stimuli (each of 200 μs duration) applied at 50 or 100 Hz during a five-second period. At **1006**, the nerve and muscle responses are recorded using the sensor electrodes **104** and **106**. At **1008**, a determination is made as to whether a predetermined number of stimuli have been applied, i.e., 250 or 500. If No, a subsequent stimulus is applied after a predetermined time interval, for example 4 ms or 2 ms, when the pulses are applied at a rate of 50 or 100 Hz, respectively, has elapsed at **1010**. If Yes, after the first stimulus is complete, a determination is made as to whether a predetermined time interval has elapsed at **1012**. For example, in one implementation, the predetermined time interval is 30 seconds. After the predetermined time interval has elapsed, at **1014**, a second stimulus is applied. For example, the second stimulus may be a single twitch. At **1016**, the nerve and muscle responses are recorded using the sensor electrodes **104** and **106**. At **1018**, a determination is made as to whether the second stimulus has been applied a predetermined number of times, i.e., 20, at a frequency of 1 Hz (1 stimulation/sec).

[0107] At **1022**, after the second stimulus is complete, a determination is made as to whether the collected data are valid, which is discussed in detail with regard to FIG. **7**. At **1024**, the amplitudes of the muscle responses are measured. At **1026**, the number of second stimuli (delivered at a frequency of 1 Hz) that elicit a non-zero response are counted. As the neuromuscular block deepens, the number of second stimuli that elicit a response decreases. In other words, the PTC value decreases for deeper levels of neuromuscular block.

[0108] At **1028**, a determination is made as to whether the stimulation mode is manual or continuous. When the stimulation mode is manual, a subsequent stimulation protocol is applied only after the user triggers application using for example, user-input controls of the control/visualization unit **132**. When the stimulation mode is continuous, at **1030**, a determination is made as to whether a predetermined time between stimulation protocols has elapsed. Preferably, the predetermined time for the PTC protocol is 120 seconds. In addition, the control/visualization unit **132** may display the time interval until application of the next stimulation protocol.

[0109] FIG. **11** illustrates a flow diagram of example operations when monitoring neuromuscular block during surgery. At **1102**, the anesthesiologist may choose a stimulation protocol such as the single twitch, the TOF, the tetanic or the PTC test protocol for use at the beginning of the surgery. Next, at **1104**, the anesthesiologist may administer the muscle relaxants in order to induce the neuromuscular block. After administering the muscle relaxants, the anesthesiologist may monitor the neuromuscular block at **1106**. For example, in one implementation, the anesthesiologist may monitor the neuromuscular block prior to intubation using the TOF protocol, and when the TOF ratio drops to zero and remains at zero for at least three consecutive readings, the neuromuscular block may be maximal. At this point, at **1108**, the patient's trachea may be intubated.

[0110] At **1110**, the anesthesiologist may again choose a stimulation protocol while reducing the dose of the muscle relaxants prior to performance of the surgery at **1112**. For example, the anesthesiologist may monitor the neuromuscular block using the TOF protocol until a minimal, non-zero TOF ratio is obtained. During the surgery, the anesthesiologist may continue to monitor the neuromuscular block at **1114**. At the conclusion of the surgery, the anesthesiologist may again choose a stimulation protocol at **1116** prior to administering reversal drugs, i.e., antagonists at **1118**. After administering antagonists, the anesthesiologist may monitor the neuromuscular block at **1120**. For example, the anesthesiologist may monitor the neuromuscular block using the TOF protocol until twitch returns and the TOF ratio normalizes to at least 0.90, and preferably 1.0. Finally, at **1122**, the breathing tube may be removed from the patient's trachea.

[0111] FIG. **12** illustrates example operations of performing the TOF test protocol prior to intubation. At **1202**, the

anesthesiologist may choose the TOF test protocol in the continuous mode. Then, at **1204**, the anesthesiologist may administer the muscle relaxants in order to induce the neuromuscular block. At **1206**, the anesthesiologist begins to monitor the neuromuscular block. During monitoring, the control/visualization unit **132** may display a bar graph indicating the amplitude of the muscle responses, the ratio, the count, the percentage block, etc. In addition, the response to each successive stimulus application may be scrolled on control/visualization unit **132**, for example. At **1208**, the patient's trachea may be intubated.

[0112] FIG. **13** illustrates example operations when performing the tetanic test protocol (TET) during surgery and the TOF test protocol after administering reversal drugs. At **1310**, the anesthesiologist may choose the stimulation protocol to be used for monitoring the neuromuscular block during surgery at **1314**. For example, when deep relaxation is required at **1324**, the anesthesiologist may monitor the neuromuscular block using the tetanic protocol in the continuous mode. When deep relaxation is not required, but the surgery is not complete at **1326**, the anesthesiologist may choose to monitor the neuromuscular block using the TOF protocol in the manual mode. At the conclusion of the surgery, the anesthesiologist may again choose a stimulation protocol at **1316** prior to administering the antagonists at **1318**. After administering the antagonists, the anesthesiologist may choose to monitor neuromuscular block at **1320** using the TOF protocol in the continuous mode. During monitoring, the control/visualization unit **132** may display a bar graph indicating the amplitude of the muscle responses, the ratio (in appropriate color), the count, the percentage block, etc. In addition, the response to each successive stimulus application may be scrolled on control/visualization unit **132**, for example. When twitch returns and the TOF ratio normalizes to at least 0.90, and preferably 1.0, the tube may be removed from the patient's trachea at **1322**.

[0113] FIG. **14** illustrates example operations when turning off the monitoring device. At **1402**, the anesthesiologist may turn off the stimulation protocol. Then, at **1404**, a determination is made as to whether the data are to be saved. If Yes, the collected data may be saved internally in the device at **1406**. As discussed above, it may be possible to download the collected data from the control/visualization unit **132** using the external communication link **124**. After the collected data have been saved or it is determined that it is not necessary to save the collected data, the anesthesiologist may turn the device off at **1408**. In some implementations, the data may be interfaced with an electronic medical record storage system for storing in the patient's electronic medical record.

[0114] FIG. **15** illustrates example operations when removing the electrodes from the patient. At **1502**, the anesthesiologist may disconnect the stimulation and sensing electrodes **102**, **104** and **106** from the stimulating/recording unit **130**. As discussed above, the electrodes **102**, **104** and **106** may be connected to the wires using a custom key. At **1504**, a determination is made as to whether additional monitoring will be required. If No, the anesthesiologist may remove the electrodes **102**, **104** and **106** from the patient at **1520**. If Yes, the patient may be moved to the recovery ward without removing the electrodes **102**, **104** and **106**.

[0115] After moving the patient to the recovery ward, a determination is made as to whether additional monitoring will be required at **1506**. If No, the anesthesiologist may remove the electrodes **102**, **104** and **106** from the patient at **1520**. If Yes, at **1508**, the anesthesiologist may connect the electrodes **102**, **104** and **106** stimulating/recording unit **130**. Then, at **1510**, the anesthesiologist may turn on the device and begin monitoring the neuromuscular block at **1512**. After interpreting the results at **1514**, a determination is made as to whether additional monitoring is required at **1516**. If Yes, the anesthesiologist may continue to monitor the neuromuscular block at **1512**. If No, at **1518**, the anesthesiologist may disconnect the electrodes **102**, **104** and **106** from the stimulating/recording unit **130**, and then remove the electrodes **102**, **104** and **106** from the patient at **1520**.

[0116] With reference to FIG. **16**, an example system for implementing aspects described herein includes a processing device **1620**. In its most basic configuration, the processing device **1620** typically includes at least one processing unit **1602** and memory **1604**. Depending on the exact configuration and type of processing device, memory **1604** may be volatile (such as random access memory (RAM)), non-volatile (such as read-only memory (ROM), flash memory, etc.), or some combination of the two.

[0117] The processing device **1620** typically includes a variety of computer readable media. The computer readable media can be any available media that can be accessed by processing device **1620** and includes both volatile and non-volatile media. The computer readable media may be stored on volatile or non-volatile memory, and the memory can be implemented in any method or technology for storage of information such as computer readable instructions, data structures, program modules or other data. Memory includes, but is not limited to, RAM, ROM, electrically erasable program read-only memory (EEPROM), flash memory or other memory technology, CD-ROM, digital versatile disks (DVD) or other optical storage, magnetic cassettes, magnetic tape, magnetic disk storage or other magnetic storage devices, or any other medium which can be used to store the desired information and which can be accessed by the processing device **1620**.

[0118] It should be understood that the various techniques described herein may be implemented in connection with hardware or software or, where appropriate, with a combination of both. Thus, the methods and systems of the presently disclosed subject matter, or certain aspects or portions thereof, may take the form of program code (i.e., instructions) embodied in tangible media, such as floppy diskettes, CD-ROMs, hard drives, or any other machine-readable storage medium wherein, when the program code is loaded into and executed by a machine, such as a processor, the processor becomes an apparatus for practicing the presently disclosed subject matter. In the case of program code execution on programmable computers, the computing device generally includes a processor, a storage medium readable by the processor (including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. One or more programs may implement or utilize the processes described in connection with the presently disclosed subject matter, e.g., through the use of an application programming interface (API), reusable controls, or the like. Such programs may be implemented in a high level procedural or object-oriented programming language to communicate with a computer system. However, the program(s) can be implemented in assembly or machine language, if desired. In any case, the language may be a compiled or interpreted language and it may be combined with hardware implementations

[0119] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

[0120] Disclosed are materials, systems, devices, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods, systems and devices. These and other components are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these components are disclosed that while specific reference of each various individual and collective combinations and permutations of these components may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed each and every combination and permutation of the method, and the modifications that are possible are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed systems or devices. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed.

[0121] Publications cited herein and the materials for which they are cited are hereby specifically incorporated by reference in their entireties.

What is claimed is:

1. A method for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent, comprising:

stimulating a motor nerve to cause an evoked muscle response;

recording the evoked muscle response, the evoked muscle response comprising a floating differential signal;

quantifying the recorded muscle response; and

comparing the quantified muscle response to a control muscle response, wherein the comparison indicates a level of neuromuscular blockade in the subject.

2. The method of claim **1**, wherein the floating differential signal is a non-ground-referenced differential signal.

3. The method of claim **1**, wherein recording the evoked muscle response further comprises:

recording for muscle electrical activity in a muscle innervated by the motor nerve using two recording electrodes; and

determining a difference between the muscle electrical activity recorded by the each of the two recording electrodes.

4. The method of claim **3**, wherein determining a difference between the muscle electrical activity recorded by each of the two recording electrodes is accomplished without recording for muscle electrical activity using a common reference electrode.

5. The method of claim **3**, wherein recording for muscle electrical activity in a muscle innervated by the motor nerve comprises using no more than two recording electrodes.

6. The method of claim **1**, wherein stimulating the motor nerve comprises stimulating the motor nerve with a repeated train of temporally-spaced stimuli.

7. The method of claim **6**, wherein the control muscle response is a quantified muscle response caused by a prior or subsequent stimulus in the repeated train of temporally-spaced stimuli.

8. The method of claim **6**, wherein the motor nerve is stimulated according to a train-of-four protocol or a tetanic protocol.

9. A system for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent, comprising:

a stimulator configured to generate one or more stimuli for stimulating a motor nerve to cause an evoked muscle response;

a patient-stimulus interface configured to supply each stimulus generated by the stimulator to the patient;

a patient-recording interface configured to record the evoked muscle response in a muscle innervated by the motor nerve, the evoked muscle response comprising a floating differential signal; and

at least one processing device configured to:

quantify the recorded muscle response; and

compare the quantified muscle response to a control muscle response, wherein the comparison indicates a level of neuromuscular blockade in the subject.

10. The system of claim **9**, wherein the floating differential signal is a non-ground-referenced differential signal.

11. The system of claim **9**, wherein the patient-recording interface comprises at least two recording electrodes for recording muscle electrical activity in the muscle innervated by the motor nerve, the non-ground-referenced differential signal being a difference between the muscle electrical activity recorded by the each of the at least two recording electrodes.

12. The system of claim **9**, wherein the stimulator is configured to stimulate the motor nerve with a repeated train of temporally-spaced stimuli.

13. The system of claim **12**, wherein the control muscle response is a quantified muscle response caused by a prior or subsequent stimulus in the repeated train of temporally-spaced stimuli.

14. The system of claim **12**, wherein the motor nerve is stimulated according to a train-of-four protocol or a tetanic protocol.

15. A system for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent, comprising:

a stimulator configured to generate one or more stimuli for stimulating a motor nerve to cause an evoked muscle response;

a patient-stimulus interface configured to supply each stimulus generated by the stimulator to the patient;

a patient-recording interface comprising at least two recording electrodes and configured to record muscle electrical activity of a muscle innervated by the motor nerve, wherein the patient-recording interface does not include a common reference electrode; and

at least one processing device configured to:

quantify the recorded muscle electrical activity; and

compare the quantified muscle electrical activity to a control muscle electrical activity, wherein the comparison indicates a level of neuromuscular blockade in the subject.

16. The system of claim **15**, wherein the recorded muscle electrical activity is a floating differential signal.

17. The system of claim **15**, wherein the recorded muscle electrical activity is a non-ground-referenced differential signal.

18. The system of claim **16**, wherein the recorded muscle electrical activity comprises a difference between the muscle electrical activity recorded at each of the at least two recording electrodes.

19. The system of claim **15**, wherein the stimulator is configured to stimulate the motor nerve with a repeated train of temporally-spaced stimuli.

20. The system of claim **19**, wherein the motor nerve is stimulated according to a train-of-four protocol or a tetanic protocol.

21. An electrode system for use with a system for assessing neuromuscular blockade in a subject, comprising:

one or more stimulation electrodes configured to deliver a stimulus to a motor nerve of the subject; and

at least two recording electrodes configured to record muscle electrical activity of a muscle innervated by the motor nerve, wherein the electrode system does not include a common reference electrode.

22. The electrode system of claim **21**, wherein the recorded muscle electrical activity is a difference between muscle electrical activity recorded at each of the at least two recording electrodes.

23. The system of claim **21**, wherein the recorded muscle electrical activity is a floating differential signal.

24. The system of claim **21**, wherein the recorded muscle electrical activity is a non-ground-referenced differential signal.

25. A system for assessing muscle electrical activity in a subject, comprising:

a motor nerve stimulator configured to stimulate a targeted motor nerve of the subject;

a recording apparatus for recording electrical activity of a muscle innervated by the motor nerve; and

a recording apparatus for recording electrical activity of the targeted motor nerve.

26. The system of claim **25**, further comprising at least one processor configured to identify whether an electrical response to the stimulus was recorded in the muscle.

27. The system of claim **25**, further comprising at least one processor configured to identify whether an electrical response to the stimulus was recorded in the motor nerve.

28. The system of claim **25**, further comprising a processing system configured to identify whether an electrical response to the stimulus was recorded in the muscle and whether an electrical response to the stimulus was recorded in the motor nerve.

29. The system of claim **29**, wherein the processing system is further configured to indicate that the nerve was not stimulated if there is no electrical response to the stimulus recorded in the nerve.

30. The system of claim **26**, wherein the subject has been administered a muscle relaxant agent.

31. The system of claim **30**, wherein the processing system is further configured to indicate the presence of neuromuscular blockade in the subject when an electrical response to the stimulus is recorded in the nerve and there is an absent or diminished electrical response to the stimulus recorded in the muscle.

32. A method for identifying whether a motor nerve in a subject has been stimulated, comprising:

applying a stimulus to the subject, wherein the stimulus is targeted to stimulate the motor nerve;

recording for an electrical response to the applied stimulus in the targeted motor nerve; and

recording for an electrical response to the applied stimulus in a muscle innervated by the targeted motor nerve, wherein the presence or absence of an electrical response to the applied stimulus in the muscle and the presence or absence of an electrical response to the applied stimulus in the targeted motor nerve is used to assess whether the motor nerve was simulated.

33. The method of claim **32**, wherein an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the targeted motor nerve indicating the motor nerve was stimulated.

34. The method of claim **32**, wherein an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve indicating that the motor nerve was not stimulated.

35. The method of claim **32**, wherein an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve indicating that the motor nerve was not stimulated.

36. The method of claim **32**, wherein the subject has been administered a muscle relaxant agent prior to application of the stimulus to the subject.

37. The method of claim **36**, wherein an electrical response to the applied stimulus is not recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve indicating neuromuscular blockade in the subject.

38. The method of claim **36**, wherein a diminished electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the motor nerve indicating neuromuscular blockade in the subject.

39. A method for assessing neuromuscular blockade in a subject having been administered a muscle relaxant agent, comprising:

applying a stimulus to the subject, wherein the stimulus is targeted to stimulate a motor nerve;

recording for an electrical response to the applied stimulus in the targeted motor nerve; and

recording for an electrical response to the applied stimulus in a muscle innervated by the targeted motor nerve, wherein the recorded electrical response of the nerve and the recorded electrical response of the muscle are used to assess neuromuscular blockade in the subject.

40. The method of claim **39**, wherein an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is recorded in the targeted motor nerve indicating that the target motor nerve was stimulated.

41. The method of claim **39**, wherein an electrical response to the applied stimulus is recorded in the muscle and an electrical response to the applied stimulus is not recorded in the targeted motor nerve indicating that the targeted motor nerve was not stimulated.

42. The method of claim **39**, wherein an electrical response to the stimulus is not recorded in the muscle and an electrical response to the stimulus is not recorded in the targeted motor nerve indicating that the target motor nerve was not stimulated.

43. The method of claim **39**, wherein an electrical response to the stimulus is not recorded in the muscle and an electrical response to the stimulus is recorded in the motor nerve indicating neuromuscular blockade in the subject.

44. The method of claim **39**, wherein a diminished electrical response to the stimulus is recorded in the muscle and an electrical response to the stimulus is recorded in the nerve indicating neuromuscular blockade in the subject.

45. The method of claim **43**, further comprising determining an amplitude of the recorded electrical activity of the muscle, wherein the determined amplitude compared to a control amplitude indicates a level of neuromuscular blockade in the subject.

46. The method of claim **45**, wherein the control amplitude is an amplitude of recorded electrical activity of a prior or subsequent stimulus.

47. The method of claim **39**, wherein the stimulus is applied during application a train-of-four stimulus protocol.

48. A method for assessing neuromuscular blockage in a subject having been administered a muscle relaxant agent, comprising:

applying a stimulus to the subject, wherein the stimulus is targeted to stimulate a motor nerve;

recording for an electrical response to the stimulus in a muscle innervated by the targeted motor nerve; and

recording for an electrical response to the stimulus in the targeted motor nerve, wherein an absent or diminished electrical response to the stimulus in the muscle and the presence of an electrical response to the stimulus in the motor nerve indicates neuromuscular blockade in the subject.

49. The method of claim **48**, wherein the stimulus is applied during application a train-of-four stimulus protocol to the subject.

50. A system for assessing muscle electrical activity in a subject, comprising:

a motor nerve stimulator configured to stimulate a targeted motor nerve of the subject, the motor nerve stimulator comprising:

a power source; and

at least one stimulating electrode; and

a recording apparatus for recording electrical activity of a muscle innervated by the motor nerve and for recording electrical activity of the targeted motor nerve, the recording apparatus including:

a power source; and

at least one recording electrode, wherein the motor nerve stimulator and the recording apparatus are in galvanic isolation.

51. The system of claim **50**, wherein the power source of the motor nerve stimulator and the power source of the recording apparatus are dedicated power sources, each providing power to only the motor nerve stimulator or the recording apparatus, respectively.

52. The system of claim **51**, wherein the motor nerve stimulator comprises no more than two stimulating electrodes, and the recording apparatus comprises no more than two recording electrodes.

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专利名称(译)	用于评估肌肉电活动响应于刺激运动神经的方法和系统		
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摘要(译)

提供了用于监测麻醉的系统，装置和方法。例如，方法，装置和系统任选地用于响应于运动神经的刺激来评估肌肉电活动。